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COWDRY'S Problems of AGEING

Biological and Medical Aspects

THIRD EDITION Edited by

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Foreword

The occasion of the publication of another edition of PROBLEMS OF AGEING under the inspiration of a new editor provides an opportunity for the retiring editor to highlight certain important developments in the field of gerontology and to acknowledge the continuing support of the Josiah Macy, Jr. Foundation to these efforts. Earlier contributions have been briefly outlined in the prefaces to the first and second editions republished herewith.

In 1945 interest in ageing on the part of investigators in biological, medical and sociological aspects of the problem, of social workers, nurses, clinical psychologists, and of administrators of welfare agencies, both private and governmental, had demonstrated the need for a multi-professional scientific society in this field and for a journal to publish results of scientific investigations. The Gerontological Society was formed in that year and, aided by a subsidy from the Foundation for the first three years, undertook to publish a journal—GERONTOLOGY—the first issue of which appeared in January 1946. The Society held its first scientific session in January 1949 with an attendance of eighty and a membership of 240, in which the several sciences concerned with problems of ageing were represented. In 1945 the Foundation assisted the Gerontological Society to form a Registry of Gerontology in the Army Institute of Pathology for the collection of tissues of animals and human beings of known age for research purposes.

Today many government grants are being made for research on biological and medical aspects of ageing by the National Heart Institute, following recommendation by the 16-member National Advisory Heart Council under the chairmanship of Dr. Paul White. A significant move was made by Federal Security Administrator Oscar R. Ewing in the appointment of a committee on Geriatrics and Gerontology, Clark Tibbits, chairman, to integrate activities within the various parts of the Federal Government and to complement activities of non-government agencies.

Representatives from fourteen nations meeting in Belgium in July 1950 agreed that a Second International Gerontological Congress would be helpful. This Congress was held in St. Louis September 9–14, 1951 with the cooperation of the U. S. Public Health Service, through the National Advisory Heart Council, and supported by a grant from the Macy Foundation. The Foundation also arranged a meeting of its conference group on ageing immediately before the Congress, at which the directors of the four Congress sections were able to visualize an harmonious and effectively integrated Congress program. This informal exchange of opinion provided

clues to some of the most important and feasible objectives in gerontology to be systematically evaluated and explored during the Congress.

It is now almost ten years since the presentations that made up the second edition of PROBLEMS OF AGEING went to the printer. The third edition, edited by Dr. A. I. Lansing, brings together recent accounts of biological and medical aspects of the problem, integrated with a number of contributions from sociological and economic lines of inquiry. New avenues of investigation have been opened and existing ones have been followed. Only a small part of the information now available, however, has been utilized to enable people to live healthier, more useful and longer lives. What may be regarded as pilot experiments in relatively concise areas of human betterment reveal that if work in this direction is dignified by public approval and support, the following decade will be one of great achievement.

EDMUND V. COWDRY

Preface to the Third Edition

In organizing and finally editing the third edition of *Problems of Ageing* my primary objectives were to render a report on what has transpired in gerontology since 1942, when the second edition was prepared, and to report the opinions of a group of gerontologists as to significant trends and profitable areas for further work on ageing.

This is essentially a progress report. No attempt has been made to influence the writings of the contributors. Indeed, in some instances the editor disagrees, in principle, with the points of view expressed, and it is quite likely that some of the contributors do not see eye to eye with the editor. The point is that an attempt is being made to convey to the reader, for better or for worse, an objective synopsis of new developments, current trends, and the thoughts of a number of the present day workers in gerontology.

In some fields of research on ageing little has transpired of note in the last decade and the contributors have so indicated. In other areas there has been considerable activity. Research on cardiovascular diseases quite properly has received marked emphasis. This class of diseases is the greatest killer in the adult population today. The role of lipids in arteriosclerosis is being followed both intensively and extensively with much yet to be done. The importance of dietary fat and of the physicochemical nature of circulating lipids in conditioning cholesterol deposition in arteries has recently been stressed. This has been set back most sharply by the observation of Siperstein that cholesterol is synthesized in the arterial wall. During the last several years the editor has placed emphasis on the role of ageing of the arterial wall in the production of arteriosclerosis. This point of view is not too well entertained.

On the whole I believe that a spirit of pessimism is present in many of the chapters. Dr. Cobb urges caution in interpretation of many of the almost classical views on ageing of the skeletal system; new data are slow in appearing. Dr. Bickerman summarizes a wide variety of diseases of the respiratory system associated with ageing and finds that the situation is confused. And so it goes.

Research on the biology of ageing is almost at a standstill. There is hardly a handful of workers in this area today. Our population is rapidly becoming an old population. There is a sense of urgency in attacking the so-called degenerative diseases which take such a heavy toll of mature and

elderly adults. It may be that the sources of funds for research are supporting clinical and allied research on ageing to the effective exclusion of biology. This may be an unwarranted suspicion; it is equally possible that were more funds available for gerontology, all areas of research, including biology, would flourish.

Throughout the book there is expressed a need for clarification of the relation between degenerative diseases and ageing. Just what do we mean by ageing and degenerative diseases? It seems that neither is well enough defined to permit a rational distinction between the two. If we accept the view that ageing begins at the time of conception, we rapidly get into difficulties. Gerontology becomes the study of the biology of living. I do not believe that gerontology includes study of the development of the foetus or of the physiologic and psychic throes of adolescence. Ageing, to my mind, is a problem of adulthood, of generally progressive deleterious change in adulthood, correlated with the passage of time. Some of these changes may be classed as diseases and may indeed be curable or reversible. Others may involve profound alterations in the physicochemical makeup of protoplasm, and as such may be irreversible. But regardless of reversibility or specific etiology, all these changes constitute ageing.

In order not to overdo the pessimistic note, it should be observed that much progress has been made in organizing and more widely establishing this relatively new science of gerontology. This point is well made by Dr. Cowdry in his Foreword. Also, the sociologists have effectively come to grips with the problems of ageing and are moving forward briskly. It is refreshing to note that compulsory retirement at arbitrarily fixed ages is being challenged.

The lot of an editor is not entirely a happy one. Credit for effective writing very properly goes to the individual authors. With equal propriety, criticism of errors or inadequacy goes to the editor. If, however, in the reading of this book new research is stimulated, I will have been rewarded.

ALBERT I. LANSING

Preface to the Second Edition

The First Edition was published in January 1939. Soon thereafter demands for more copies were met by a reprinting of the book in which it was not however possible to make either corrections or additions. This favorable reception indicates an increasing consciousness of the inevitability of a further rise in age level of the population and of the necessity of facing it in a constructive way. Our principle of mobilizing and integrating the knowledge and experience of specialists in different fields has been widely followed as is evidenced by the arrangement of symposium after symposium on the subject of ageing. *Of these the following is a partial list:*

Medical Clinics of North America (Med. Clin. North Am., 1940, 24, 1-164).

American Orthopsychiatric Association (Am. J. Orthopsych., 1940, 10, 27-86).

University of Pennsylvania Centennial Celebration, September, 1940.

Massachusetts Society for Research in Psychiatry—The Symposium dealing with the problems of the aged (Taunton, Mass.), October 11, 1940.

National Institute of Health (Washington), May, 1941.

American Chemical Society (Atlantic City), September, 1941.

Chicago Medical Society, December, 1941.

As the data from the 1940 census have become available we see more clearly the importance of the problem before us from points of view too numerous to mention. One of these is the mobilization of an increasingly large percentage of older people in the war effort, and also for the postwar reconstruction. It is interesting to note that the percentage of those of 65 years and over, calculated in advance for 1940, was surpassed.

Since the publication of the first edition three definite steps have been made to organize research on ageing. Encouraged by the Josiah Macy Jr. Foundation and with the aid of Dr. E. J. Stieglitz, Surgeon General Parran has appointed a National Advisory Committee on Gerontology and authorized a nation-wide survey of investigations on ageing by the U. S. Public Health Service. This fact finding and coordinating function has been supplemented by reorganization of the National Research Council's Committee on Ageing, under the chairmanship of Dr. A. J. Carlson, of the University of Chicago, as a fund raising agency and planning group to further re-

search on ageing. Situated also in Washington, closely affiliated with the National Academy of Sciences and representative of the whole country, the Council is better able to serve in this important capacity than any other organization. A third group concerned with research formulations and action has been established by Dr. V. Korenchevsky who visited the United States for that purpose. It is the American Branch of an International Club for Research on Ageing and operates under the presidency of Dr. Wm. deB. MacNider of the University of North Carolina at Chapel Hill. This club is a small group of investigators each of whom devotes a large part of his time to investigations on the many sided problems of ageing. The idea is that from this very active nucleus the impulse to research will spread widely throughout the United States aided constructively by the U. S. Public Health Service and the National Research Council.

Since these three groups have held frequent meetings, often made possible by the Josiah Macy Jr. Foundation, and because many members of each are also contributors to this volume, ample opportunity has been afforded for the exchange of ideas. An effort has been made to include 9 new chapters without greatly increasing the size of the volume. Consequently in revising and bringing up to date the chapters in the first edition considerable abbreviation has been necessary. The editor is indebted to the authors for their friendly cooperation. He records with deep regret the death of Dr. Ludwig Kast, under whose far-sighted and inspiring leadership this venture was launched, and of Dr. T. Wingate Todd who played a prominent part in the writing of the first edition. He gratefully acknowledges, on behalf of all of the contributors, the continued and very helpful interest of Mr. Lawrence K. Frank and Dr. F. Fremont-Smith, both officers of the Josiah Macy Jr. Foundation.

E. V. Cowdry

St. Louis,
July 15, 1942

Preface to the First Edition

This volume is a timely and logical development of the survey of the problem of arteriosclerosis[1] which was published by the Josiah Macy, Jr. Foundation in 1933 to summarize existing knowledge on the degenerative changes and ageing of blood vessels. When the present volume was well under way, the Foundation provided for a conference on ageing, jointly sponsored by the Union of American Biological Societies and the National Research Council, at Woods Hole on June 25 and 26, 1937, which was attended by fifteen of the contributors to this volume as well as by other interested persons. The National Research Council also arranged a conference of its Committee on the Biological Processes of Ageing in Washington, D. C. on February 5, 1938 which included in its attendance seven contributors to this volume. Other smaller meetings of contributors, interested in the ageing of the nervous system and of the endocrines, were arranged by the Foundation. Abstracts and complete manuscripts have been circulated widely among the contributors. Consequently, the opportunity to bring to bear on the problem the experience and points of view of many specialists, working together in a constructive way, has been unrivaled. But each contributor is personally responsible for his chapter. There are, as one would expect, some differences of opinion. These foreshadow progress since they will stimulate further investigation. The style is as simple as possible consistent with scientific accuracy. Each chapter concludes with a summary and a bibliography. The editor feels much indebted to Dr. Ludwig Kast, Mr. Lawrence K. Frank and Dr. F. Fremont-Smith of the Josiah Macy, Jr. Foundation for their continued interest and support. To the contributors of this volume he wishes to express his thanks for their cooperation.

E. V. Cowdry

July 22, 1938

[1] Arteriosclerosis: A Survey of the Problem. Edited by Edmund V. Cowdry. The Macmillan Company, 1933, New York.

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Introduction

It is a privilege to be asked to write the Introduction to the third edition of *Problems of Ageing*, originally published in 1939. This new edition, as in the case of the first and second, must inevitably raise more questions than it can answer. Such, however, is the way of all explorations at the frontiers of knowledge, and should occasion neither surprise nor chagrin.

What do we mean by ageing? Can we define the term, and separate the pathological conditions which accompany old age from the normal processes of senescence?

Even such fundamental issues as these cannot yet be settled with any degree of satisfaction, perhaps because they impinge upon the basic question of the nature of Life itself—growth, development, maturation and ageing representing but subdivisions of the life process.

An aged plant, animal or human being is obviously different from a younger member of the species—but to what extent do the gnarled bark of a tree, the quality of fur and teeth of a dog or the characteristic appearance and behavior of an elderly man or woman reflect the intrinsic (and hence, perhaps, inevitable) changes which accompany the passage of time; and to what extent are they merely scars of accidental (and hence, perhaps, *preventable*) traumata resulting from an adverse environment?

If we wish to discuss normal senescence, must we not define what we mean by "normal"? Normal with respect to what? Do we mean by "normal" the average, or the optimum—and if the latter, must we not still ask the question, "Optimum with respect to what?"

Beginning in childhood, the "normal" kidney quite regularly shows a few necrotic glomeruli. These increase in number with age. We say that such a kidney is "normal", but are the necrotic glomeruli "normal"? The question cannot be answered "yes" or "no". With respect to other living glomeruli, those that are dead or dying are grossly pathological; but it is nevertheless quite "normal" for the kidney of a twenty-year-old man or woman to show a few dead glomeruli. Such dead glomeruli we accept as normal in 1952, but fifty or one hundred years hence will the kidneys of young adults show such necrotic glomeruli, or so many?

During the first two months after birth the human adrenal goes through a process of involution, with a 30 per cent reduction in weight. During each estral cycle both ovarian and uterine arteries participate in a very active process of involution. Could the study of such involutionary changes throw light upon the ageing process?

We are apt to say that for each organism there is a life span which is

not likely to be greatly extended; but do we overlook the continuation of the species through the germ plasm? Does the germ plasm age? Is the process of evolution itself an indication of ageing of the germ plasm? What, indeed, *do* we mean by "ageing"?

One thing seems clear: that the study of a physiological function or anatomical structure may be quite different, depending upon whether the study is focussed upon the "ageing" of the function or structure, or upon some other aspect such as the susceptibility to disease or the response to hormonal stimulation. Research in the field of ageing approaches organs, tissues or functions with a particular frame of reference. It is only in an appropriate frame of reference that facts pertinent to gerontology are likely to be revealed. Research directed at the ageing process, therefore, should not be confined to certain organs or to certain age periods, but rather should be defined by the investigator's particular interest in the ageing process.

Research in ageing is not likely to be rewarding if it is a secondary issue in the course of another research. Research in this field, as in the field of growth, is a special problem requiring its own method of attack, a time-span during which the ageing process is observed, and financial support of sufficient duration to cover the appropriate time-span.

The demand for a third edition of this volume is an indication of the widespread and growing interest of biologists, physicians and social scientists in the latter portion of the life span. This interest springs from theoretical and also from very practical considerations.

As a larger and larger proportion of the population of a country receives the benefits of modern advances in preventive and therapeutic medicine, there is a progressive increase in the average life expectancy and *pari passu* an increasing proportion of the population in the older age ranges.

There are a number of consequences: an increase in the incidence of the diseases and disabilities of later years, a new interest on the part of physicians in the treatment of older persons, and new opportunities and responsibilities for research into the causes, treatment and prevention of such conditions.

The sociologist, the industrialist, the labor leader, as well as the community as a whole and the individual families thereof, are involved in such increase in the average life-span.

There are problems of housing—modern dwellings make no provision for long-lived grandparents—and of retirement. Must retirement be abrupt, as at present, or is a "progressive" or "graded" retirement practical? Here management and labor have an opportunity to make pilot studies before the growing number of employable but unemployed "oldsters" become politically organized.

Many of these questions, and others which will occur to the reader, must remain unanswered at this time; but they constitute an urgent challenge—one which justifies and requires sustained and intensive multiprofessional research at the biological, medical and social levels, with the goal that each individual during his life-span may more and more completely fulfill his highest potentialities.

New York, N. Y.

FRANK FREMONT-SMITH, M D.
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Section I

CHAPTERS 1 TO 7

BIOLOGICAL AND CELLULAR PROBLEMS OF AGEING

1

GENERAL PHYSIOLOGY

A I LANSING

St Louis

Concepts of Ageing

"If we were to view 'natural death' as the termination of existence due to the uniform senescent atrophy of the organism, leading to a uniform depression and ultimately simultaneous extinction of all its functions, then 'natural death' in all probability never occurs. In a world in which the organism could be completely shielded from fortuitous strains and the invasive activities of parasitic organisms, the phenomenon of 'natural death' might conceivably occur. In actuality death is always in some measure accidental. Thus an aged individual contracts pneumonia and succumbs to its effects. Death is, in its immediate origin, attributable in this event to the invasion of parasites which are accidentally encountered.—Similarly when rupture of a cerebral vessel due to arteriosclerosis occurs, the existence of all parts of the body may be terminated by this 'accidental' event, but its ultimate origin is the general senescence of the tissues, of which arteriosclerosis is merely one particular manifestation." This point of view expressed by Robertson (81) in 1923 is as pertinent today as it was then. It does not, however, aid us to characterize what is referred to as general senescence of tissues.

For a general introduction to the biological aspects of ageing the reader is referred to several books which quite adequately express the views of the twentieth century. Robertson's volume, already mentioned, stresses the antithesis between growth and ageing (81) Minot's book (70) expresses the thinking of the morphologist; he develops the concept of cytomorphosis and the significance of changing nucleocytoplasmic ratios in senescence) The volume by Child (19) is excellent in that it objectively reviews the theories of ageing that existed at the turn of the century, and

Based in part on a review in *Physiol. Rev.*, 31: 274-284, 1951.

presents experimental data to reinforce the author's view that longevity is closely linked to the metabolic activities of the cell. Heilbrunn's chapter on age and death (32) is particularly useful in that it is concise and well documented. Molisch (71) has prepared an excellent account of ageing in plants in a book entitled *The Longevity of Plants.*

There is a surprising lack of variety in the theories of ageing expressed during the last fifty years. Many, directly or indirectly, attribute ageing to a poisoning or intoxication of the cell. Most of these are reviewed in Child's book. T. H. Montgomery, the eminent zoologist, proposed that metabolic waste products of a toxic nature accumulate in the tissues through faulty excretory processes to effect a true intoxication and ageing of the organism. The same point of view was urged by Jickeli who went a bit further to speculate that metabolism is an incomplete process and, as a consequence of the incomplete utilization of materials, toxic materials gradually accumulate in the cell. This theory is not unlike Child's who believed that senescence results from accumulation of toxic substances in the cell and that rejuvenation is effected by their elimination. Benedict attempted to place the intoxication theory on a physicochemical basis by suggesting that the permeability of the cell is decreased with age with a consequent retention of metabolic by-products. His experimental data on permeability decrease with age have not been well supported. Lansing (54) adopted this general view of ageing and proposed that an increase with age in the calcium content of the cell cortex could be expected to lower the permeability of the cell to many substances which might interfere with metabolism of the cell. Molisch (71) was also impressed with the possibility that in plants the deposition with age of calcium in cell membranes might lower the permeability of cells to produce ageing. Heilbrunn (32) apparently falls in line with the intoxication theory of ageing. He observed that "Typically, the living organism has no means of getting rid of insoluble materials which may be deposited within its cells and this may be an important factor in the ageing process."

Metchnikoff created a flurry of interest in the intoxication theory shortly after the turn of the century with his notion that poisons derived from intestinal putrefaction are responsible for ageing. His answer to this problem was alteration of the bacterial flora of the intestine by copious intake of bacteria of the genus Lactobacillus. The theory and prophylaxis, although entirely inadequate, have been repeatedly reindorsed throughout the years. It is hardly necessary to point out that there are numerous organisms without large intestines that grow old and die.

A number of workers including Herbert Spencer and Muhlmann have stressed the point that changing relations between cell volume and cell surface limit the potentialities of the cell. It is true that as the cell grows

its volume changes far exceed the surface changes. This may well limit the amount of materials taken into the cell. Careful cytological and physiological exploration of this possibility is indicated.

The point has been repeatedly made, notably by Delage, Jennings and Cowdry, that ageing is a consequence of differentiation. This is indeed true but not too helpful in exploring the nature of ageing; it merely restates the case. Growing or intermitotic cells, as Cowdry has indicated, do not age; it is the non-growing, differentiated (post-mitotic) cells which age. Minot's theory of cytomorphosis also emphasizes the factor of differentiation in senescence via changing relations between the nucleus and cytoplasm.

Parallels have been frequently drawn between biological ageing and the ageing of colloids. Rusicka, Marinesco, Ehrenberg, Dhar and many others have written extensively on this subject. The fact is that protoplasm is in a perpetual state of flux; there is a constant turnover of its constituents by destruction and replacement of individual molecules. Thus, the colloid molecules of the old organism are newly formed but are different from those of the young. This is not true of test tube colloids in which the molecules do not turn over. The old organism does not contain old colloids, it contains newly formed colloids of an old character.

These for practical purposes are the principal theories of biological ageing. At best they are expressions of the opinions of individuals and are not too solidly based on experimental data. The fact is that we know very little about ageing.

Cell Physiology

What is ageing? When does ageing begin? What cellular components are affected by the ageing process? Is ageing an inevitable feature of life? What are the age changes which bring about the ultimate death of the organism? We do not have even the beginnings of answers to any of these questions. Yet to proceed in an orderly manner toward an understanding of senescence (or ageing) it is essential to know what one means by the term. Certainly this is an affliction of the adult the sequel to which, sooner or later, is death.

In a rough way, senescence may be correlated with the passage of time (10). For the human it is reasonable to expect that during the fourth dec-
ac [illegible]
ar [illegible]
in [illegible]
changes which [illegible]
Yet, it is seldom if ever that death can be attributed specifically to senility (92). Frequently a fall resulting in a bone fracture, a respiratory infection,

or a severe emotional shock proves sufficient to snuff out the life of the senile person. Cardiovascular diseases take an ever mounting toll of the ageing population. Nevertheless, ageing can hardly be defined as a progressive failure of the cardiovascular system since there are many organisms which grow old and die but which do not possess a self-contained circulatory system.

Analogies have frequently been drawn between the process of ageing and the wearing out of mechanical devices. Such analogies are justifiable insofar as they suggest an experimental analysis. The feeble old man may well be likened to a worn out automobile motor; he is not unlike a clock in which the spring has run down, nor unlike a worn out old shoe. The old organism is certainly worn out, it has expended its capacity for vigorous activity. But why should this be? That a piston ring of an automobile motor should wear out with use and with the passage of time is entirely reasonable and is to be expected of a material which is exposed to attrition and which cannot reconstitute itself. This situation does not carry over to the vital system.

An essential property of the living system is its ability to maintain itself, to repair and reconstitute itself. This capacity for self synthesis sets off the living from the non-living. If then the living organism can and does reconstitute itself continuously, how can it wear out? It is necessary to postulate that the wearing out or ageing process involves a decrease in efficiency of the mechanisms for reconstitution.

At the moment, ageing can be defined only in very general descriptive terms. It may be defined as a process of unfavorable progressive change, usually correlated with the passage of time, becoming apparent after maturity (51), and terminating invariably in death of the individual. That ageing is intimately and conversely related to growth has long been recognized (70, 19). However, this relationship is complex (44). In protozoa, individuality is lost by division into daughter cells (44). Successive generations and populations of the daughter cells show species differences in senescence or lack thereof. According to Jennings, some continue indefinitely with no apparent decline in vigor and in the absence of nuclear reorganization (autogamy or conjugation); some gradually do decline (become senescent) but are revitalized by nuclear reorganization; lastly some become senescent, do not undergo nuclear reorganization, and die.

Selection procedures in isolation cultures of P. aurelia result in establishment of lines of paramecia in which nuclear reorganization is markedly delayed. In such lines, carried for four to five months and through three to three hundred and fifty fissions without nuclear reorganization, death follows (95). Apparently then, cell division alone, in some protozoa, is insufficient to ward off senescence.

Among the invertebrates there are two generalized growth patterns: determinate and indeterminate, and ageing characteristics are quite different in these two (44). Determinate growth is exemplified by the multicellular rotifer. In this organism cell division ceases during embryonic life and further growth is by increase in cell size which ceases essentially at the time of sexual maturation (52). The period of vigorous adulthood is brief and is followed by senility and death (42, 43). Regeneration generally does not occur.

Flatworms such as Stenostomum are examples of indeterminate growth. New individuals arise from adults by fission. In such organisms, as in some protozoa, it would appear that senility is averted by continued division. This is not entirely the case (94). Fission in *S. incaudatum* results in the anterior segment retaining the major portion of the nervous system and essentially little need be regenerated but the tail. The posterior segment must regenerate most of the body organs including the nervous system. Sonneborn demonstrated quite effectively that, in such vegetative reproduction, lines of daughter animals from anterior segments which undergo little cell multiplication rapidly age and die. The lines from posterior segments, however, whose members must regenerate a large portion of the body, are essentially immortal.

Is there an antithesis between growth and ageing in organisms such as the rotifer which manifest determinate growth and higher metazoa which contain both growing and non-growing tissues? A number of experiments deal directly with this question.

Early experiments utilizing Drosophila (77) indicate that prolongation of the period of growth also resulted in prolongation of the life span. Semistarvation of Cladocera (42) by dilution of the infusion medium with pond water results in extension of the total life span, again by extension of the growth period. On the basis of starvation experiments on caterpillars, Drosophila and tadpoles it was concluded (47) that prolongation of the total duration of life is effected by extension of the growth period. Starvation or semistarvation result in increased longevity of protozoa (86), silkworms (46), mice (102, 81) and rats (80, 17, 103, 90).

These experiments have been highlighted by the remarkable studies of McCay and his associates (68). Rats were raised on a diet containing all of the essential nutritional materials but lacking sufficient calories to promote growth and maturation. Rats were maintained on the growth-limiting diet for 766 and 911 days after which time an increased caloric intake was able to initiate rapid growth. These previously retarded rats lived as much as 200 days longer than their controls. It would appear that as long as the growth potential exists there is no ageing.

Ageing of the parthenogenetic rotifer involves a transmissible, cumula-

tive and reversible factor (51) which makes its appearance at the time of cessation of growth of this organism (52). Less than full grown rotifers do not contain this ageing factor. The data indicate that ageing is a by-product of changes which occur in the cell at the time of growth cessation. These will be discussed in further detail subsequently.

Further it seems that the ovum is not immune to age changes; on the contrary, the physio-chemical organization of the ovum is dependent upon the age of the individual and that longevity of the individual produced from such an ovum is strongly influenced by this nongenic factor. Indeed, longevity is not the only vital trait influenced by maternal age. Methylcholanthrene-induced sarcomata appear more rapidly in litters from old parents than in litters from the same parents when they were young (99). A later study based upon litter seriation showed that although tumors appear earlier in late-born mice, these tumors tend to be less invasive (100).

Incidence of spontaneous mouse leukemia is conditioned by age of the mother (64). The older the mother the greater the resistance to leukemia in the F_1 generation. The maternal factor is not found at earliest sexual maturity. Maternal age also influences the expression of a gene for polydactyly in mice (36), and similarly influenced is hatchability of Rhode Island Red poultry (31). Curiously enough, some plants lend themselves well to study of physiological ageing (5). Experiments with the common duckweed indicate that either a growth-inhibiting substance accumulates with advancing age of the frond or else that a growth promoting substance is progressively lost. The studies of Lansing (51, 52) on the transmissible ageing factor, if pertinent here, would support the former possibility.

Cell multiplication

Much attention has been directed to characterization of age changes in the ability of cells to grow by increase in either volume or number (70, 19, 75). Recent studies (75, 74) on crustacea indicate that the rate of regeneration of limbs decreases progressively with age. "The rate of decline is much less than that of normal growth rate. The rate of decline itself declines with age."

In the mouse a decrease in mitotic activity has been described (16); the rare mitotic figures found in adult liver are concentrated about the central vein (101).

A thorough study of postnatal growth and mitotic activity of the liver of the albino rat offers some interesting data (69). Mitotic activity is largely an embryonic event. At two months of age mitoses are very scant. Binucleate cells are frequent in early life (in the intermediate third of the

liver lobule) but fall off in older animals. Polyploid cells correspondingly increase.

Although mitotic activity in liver falls off with age regenerative capacity persists (15) indicating a latent growth potential in hepatic cells. Since, in the old, liver mass is regenerated with a lag in cell production the growth potential may be considered to be reduced.

These morphologic studies have been confirmed by an ingenious physiologic experiment (67). Following removal of portions of the rat liver, P^{32} as Na_2HPO_4 was administered. The P^{32} uptake was found to decrease with age.

Apparently nuclear size is greater in adult pigs than in early postnatal animals (107). Chromosomal volume tends to increase in maturity and old age in both liver and kidney cells (11).

A comprehensive analysis of binucleate cells in mouse liver indicates that such cells decrease with age (109) and are a product of nuclear division in the absence of cytoplasmic division (9).

These various studies suggest a progressive change in the growth capacities of liver cells with age manifested by, a) embryonic active cell multiplication by mitosis, b) postnatal reduction in cytoplasmic division with substained nuclear division (giving rise to binucleate cells), c) adult reduction in nuclear as well as cytoplasmic division giving rise to polyploid cells and hypertrophic nuclei (growth progressing by increase in volume rather than by multiplication).

Nucleic acids

How the changing growth characteristics of ageing tissues are reflected in alteration of their nucleoproteins (quantitatively or qualitatively) is still a confused issue (89). It is generally agreed that high concentrations of nucleic acid are associated with active protein synthesis (growth) (13, 18). This relation is clear in contrasting embryonic and post-embryonic tissues (24, 25).

A decrease in nucleoprotein with increasing age of the lymphatic system of the rat has been described (4). A more complete histochemical survey on a number of rat tissues including liver indicates a startling lack of change with age in not only total nucleoprotein but many other tissue components (63). The concentrations of total phosphorus, acid-soluble, *lipid*, *ribonucleic acid*, and of desoxyribonucleic acid-phosphorus in young and old mouse livers were analyzed and indicated no significant differences (89).

Using P^{32} as a tracer it has been shown that the turnover of DNA (desoxyribonucleic acid) is much less than that of RNA (ribonucleic acid) (14, 30). In protozoa (91) the RNA has been described as a labile cell

component in contrast to the DNA which is stable. N^{15} is poorly incorporated into the liver DNA of rats and pigeons (23) and labelled adenine incorporated in DNA is only 1 per cent of that of RNA (29).

Here then is a situation of some interest. Analytical procedures as far as they have gone seem to indicate little quantitative change in nucleic *acids with age. Further, turnover studies indicate that ribonucleoprotein* is actively exchanged but that desoxyribonucleoprotein is a relatively inert and stable component of the nucleus (except during mitosis).

As a cytologist I am frequently impressed by the occurrence of hypertrophied and hyperchromatic nuclei in ageing mammalian cells (cardiac, muscle, liver, etc., see reference 69). A strong point has been made of the *observation that nuclear volume, in at least some organisms, increases* with age (20). The opposite view is taken by Minot (70) in his classical studies on cytomorphosis. Nucleo-cytoplasmic ratios have been studied carefully with inconclusive results by Dawborn (26). Much of the older and controversial literature has been reviewed (22, 108). What is probably true is that in some cells, such as epidermis, ageing is accompanied by decreased basophilia or loss of DNA while in others, such as cardiac muscle fibers, there is an accumulation of DNA (increased nuclear volume and/or basophilia). Nucleic acid determination on whole tissues cannot clarify this problem because of the changing population density of cells with age. It is necessary to determine the DNA concentration per nucleus.

Cytoplasmic changes

The situation as regards changes with age in the chemical structure and function of cytoplasm is particularly ill-defined. To a large extent this is due to a lack of objective data. In general one gets the impression that insoluble compounds tend to accumulate in cytoplasm with age (32). That pigment granules tend to accumulate with age in nerve cells of the bee and human has long been known (35). Indeed some of the older *theories on the nature of ageing implicated the pigments that increase* with age (73, 72). As might be expected, there are at least several types of cytoplasmic pigments which accumulate with age and with disease (21, 40). Yellow pigments increase with age in the nerve cells of man (110). These pigments are a common occurrence in ganglion cells, after thirty years of age, beginning first as a perinuclear cap but gradually extending throughout the cytoplasm (48). Whether or not these are true age pigments has been discussed by a number of workers (48, 104, 40, 65, 3). A more recent analysis of age pigments on human cardiac muscle would indicate that this acid-fast, extremely insoluble pigment is not the same as that found in vitamin E deficiency and is probably a true ageing pigment.

Significance has been added to these pigment granules by the observa-

tions of Payne (78). Cytological analysis of the age changes in the anterior pituitary and adrenal glands of the fowl reveals the presence of numerous pigment granules. "The probability is that these pigment granules (in the adrenal), as in the acidophiles of the pituitary, arise from mitochondria." These observations are supported by a recent study on age changes in the adrenal gland of the rat (41). It is indeed to be regretted that more data are not available on the age changes in mitochondria which play such an important role in the metabolism of the cell.

Since calcium tends to form insoluble compounds it is not at all surprising to find that this physiologically important ion quite generally tends to accumulate with age.

In his excellent book on longevity of plants Molisch (71) repeatedly cites evidence for a trend to calcium deposition with age. He further suggested that there might be a relation between this phenomenon and a possible decrease in cell permeability. The localization of calcium in cells of the water plant, Elodea, was determined by immersion of leaves in sodium oleate. Characteristic crystals of calcium oleate formed at the cell membranes and the concentration of the crystals there increased with age (1).

By means of electrical stimulation of the leaves of *Elodea canadensis*, insoluble crystals of calcium oxalate were formed in the central vacuole of cells of different ages The amount of cortical calcium per unit of cell surface increased with age (54).

An increase with age in the amount of calcium concentrated at cell surfaces was demonstrated by means of the microincineration technique in the various cells of a rotifer and flatworm and in the skeletal muscle fibers of the toad (55).

Calcium increases with age have been found in the brain of the guinea pig (76), sclera of the cat (96), arteries (34), elastic tissue (50), kidney (105), heart (7), and a variety of human tissues (93). A general trend to a shift with age of calcium from bone to soft tissues has been set forth (2). Lack of change with age of calcium has also been reported (63). There is some indication that the calcium increase with age is paralleled by a decrease in concentration of magnesium (27) but this observation has not been confirmed.

A physicochemical basis for intracellular calcium increase with age may be derived from turnover studies (57). Ca^{45} as $CaCl_2$ was administered intravenously to mice. The livers were extirpated at various time intervals and the specific activities of Ca^{45} in both the free and bound fractions (by ultrafiltration) were determined. The data indicate that calcium in old liver is more firmly bound than in young liver as evidenced by a much lower turnover. There is some reason to believe that intracellular calcium

is, at least to some extent, associated with a ribonucleoprotein complex located at the cell surface (57, 62, 60). Diametrically opposed to this senescent pattern is the observation that in a rapidly growing malignancy the base-binding capacity of an organic fraction is sharply reduced (61). The rapidly growing malignancy is also characterized by its inability to take up Ca^{45} from circulating blood (59).

Arterial elastic fibers, which in youth are entirely mineral free, take up with advancing age progressively greater amounts of calcium (58). Chromatographic (two dimensional paper) analysis and microbiological assay of the amino acid composition of young and old defatted elastin reveal a sharp increase with age of aspartic and glutamic acids. The greater amounts of these dicarboxylic amino acids may account for the increased affinity for calcium (58). It is possible that the age alteration in the amino acid composition of the elastic fiber may be a reflection of an age change in the chemical make-up of the fibroblasts under whose influence the fiber is formed.

Under experimental conditions there are a few experiments which again implicate calcium in ageing. Reduction of the calcium content of the medium (sea water) results in significant extension of the viability of unfertilized eggs of the sea urchin, Arbacia (87). One might properly object that viability of unfertilized ova is not comparable to longevity of adult organisms. Schecter (88) has, nevertheless, reached the conclusion that ageing of the egg is associated with an accumulation of calcium in the cortex of the egg.

Reduction of the calcium content of the medium in which rotifers are grown (in isolation culture) effects a significant extension of life span (50). Similarly, removal of calcium from the cells of the rotifer by means of transient immersion in 0.5 per cent sodium citrate results in more than a 50 per cent increase in life span.

General

As indicated in an earlier review of the subject (53) the age changes in permeability of cells have been poorly characterized except for a few plant cell studies (106, 66). Osmotic resistance of human erythrocytes, as measured photometrically after exposure to hypotonic solutions, shows significant age changes (28). Three hemolytic solutions were used; erythrocytes of children less than ten years of age manifest greater osmotic resistance than those of adults when exposed to 0.18 M glycerol in 0.36 per cent NaCl, the age differences in osmotic resistance are less marked in 0.24 M thiourea in 0.18 per cent NaCl and are minimal in hypotonic saline. Osmotic and mechanical fragility of the dog erythrocytes labelled with radioactive iron

vary with the age of the cell (97). Newly formed dog red blood cells are characterized by a greater osmotic fragility than is found in old cells. The mechanical fragility of old cells, however, is greater than that of young ones. Microphotometric measurement of the water uptake of young and old rodent root hair cells indicate a decrease with age of water uptake per unit surface area and per unit time (83).

Working with rat tissue homogenates of brain and liver, an opening wedge was driven into the problem of carbohydrate metabolism and enzymatic activity in ageing (79). Respiration of brain is constant through two years and then declines. Anaerobic glycolysis falls off after 2 to 4 months of age. No significant age changes in carbohydrate metabolism of liver were found.

Analysis of bovine articular cartilage reveals a 75 per cent decrease in cell content with age. The glucolytic power of cartilage cells is not affected by age but there is a loss of respiratory power (84). However, there is no measurable decrease in dehydrogenatic activity with age and the authors conclude (85) that the decline of respiratory activity is due to "failure of the oxygen-activating component of the respiratory system" (Histochemical determination of acid phosphatase in human senile brains gives the impression of increased amounts of this enzyme in the aged (45)) As the author recognized, quantitative estimation of phosphatase in a tissue section is, at best, difficult.

The observation by Hevesy (33) in sunflower leaves of a decrease with age in the rate of renewal of protein (using N^{15} as a labelling agent) is consistent with the general view of decreased metabolism with age. Water-insoluble carbonyl groups may be detected histochemically by the use of fuchsin sulphurous acid or 2,4-dinitrophenylhydrazine (2). The staining of a number of mouse organs with these reagents shows a decreased intensity of reaction with advancing age. The implication is that this age change may be a function of decreased physiological activity.

Direct chemical analyses on whole tissues and organs are not too revealing. Analyses of the effect of age on the amino acid composition of mammalian and human brain proteins indicate no significant shift of amino acids with the possible exception of histidine which seems to be lower in youth (12). Loss of water with advancing age does not occur in the gastrocnemius muscle of the albino rat (37). Muscle creatine is stable after maturity as is blood sugar and the equilibrium between blood and muscle lactate (37, 38).

Using histochemical procedures it appears that the liver, brain and kidney of the rat remain stable throughout life as regards phosphorous (acid-soluble lipid, etc.), chloride, and minerals (63). These results may

be conditioned by the statistical problems inherent in the method. More precise localization of the entities to be analyzed and quantitation thereof may yield very different data.

The Ageing Factor in Rotifers

In an earlier section reference was made to experiments on rotifers which indicate that an ageing factor is transmitted through the egg to influence longevity. This factor has been described as transmissible, cumulative and reversible (51, 52); apparently less than full grown rotifers do not contain the ageing factor. The essential point is that in the presence of constant genetic constitution and environment, longevity may vary as the result of shifts in properties of the cytoplasm or extra-genic environs.

Because of relative obscurity of the rotifer it would be well to give a brief description of this organism. The rotifer is a microscopic fresh water organism most frequently found in stagnant ponds that abound in infusoria. Roughly several hundred to one thousand cells are contained in the body, which varies from one quarter to one millimeter in length.

The phylum Rotatoria, or Rotifera, is distinctive in that the male when present is degenerate, lacks an alimentary tract, and lives but twenty-four hours. However, in many species, the male has never been observed. *Philodina citrina* is apparently an example, since in all of the work done during these investigations no males have appeared.

While some rotifers are sessile, creep like leeches, or swim incessantly, the entire phylum is characterized by possession of a ciliated corona at the anterior end of the body. A variety of organs is contained within the minute body of the rotifer. In addition to the ciliated corona, there is a primitive brain, so-called eye spots that may be light sensitive, flame cells, muscle fibers, a well differentiated alimentary tract, and an ovary.

Under favorable conditions, in the species currently being used, only female parthenogenetic eggs are laid which hatch in about twenty-four hours. After a period of immaturity which varies with the species, the rotifers lay eggs at the rate of one to five per day (fig. 1).

The senile rotifer is characterized by very low or no egg production, a sharply decreased rate of ciliary beat, slow passage of food through the alimentary tract, shrinkage of the ovary, and a change from clear, highly refractile tissue to opaque, dull yellow tissue.

The details of technique in the rotifer studies are rather simple. The animals were raised in isolation culture using artificial pond water as the medium. Salt concentration and hydrogen ion concentration were regulated as was temperature. The food material consisted of pure strain algae grown on agar and transferred to salt solution and fed in excess to the rotifers.

A pure clone, of necessity genetically homozygous, served as the start-

ing colony. Two divergent genealogical lines were established and maintained. On the one hand eggs were selected from adolescent mothers to establish a first generation of early born rotifers. This procedure of selecting eggs from adolescent mothers was continued through a long series of

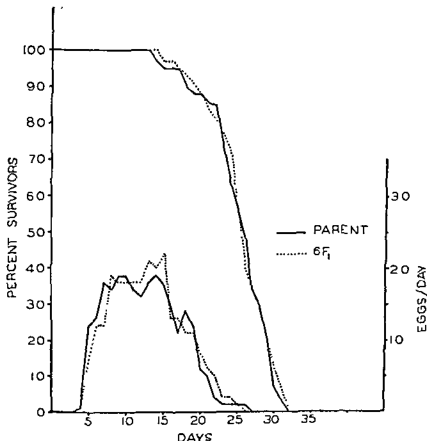


Fig. 1. Survival and egg production curves for two closely related groups of *Philodina citrina*.

generations. In contrast to this group of generations with young parentage in each generation, a contrasting series was established with almost senile parentage for each generation. The term orthoclone was designed to describe a series of generations with constant parental age through the generations.

In a senile orthoclone the mean life span of each successive generation was decreased to the point of extinction of the series (fig. 2). The acceleration of senescence by the selection of old mothers as a source of eggs for a

daughter generation could be halted and, indeed, reversed by the simple expedient of altering the selection technique to the use of *young mothers.*

Conversely, in an adolescent orthoclone the mean life span of successive generations increased steadily. Thus, using Philodina as the experimental animal, life spans increased from 24 days in the parental stock to over 100 days in the 49th generation (fig. 3).

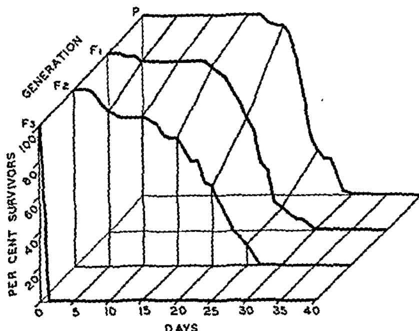


FIG. 2. Three dimensional graph to illustrate changing survival curve properties in an old orthoclone. Significant changes are present in the F_2 data and the F_3 *is essentially non-viable.*

A number of variations of the above experiments have been performed and published (51, 52). The acceleration of ageing observed in rotifers derived from senile mothers *is not restricted to the very old.* Middle-aged and even young, full grown rotifers contain the ageing factor as indicated by accelerated ageing in the progeny (fig. 4). It is only the adolescent, actively growing rotifer that does not contain the ageing factor.

Some indication of the close relation between growth and ageing can be obtained from examination of the growth characteristics and longevity of orthoclones of both young and old animals. Age of sexual maturation as measured by egg laying is used as an index of the growth rate. Figure 5 contains a summary of data in an old orthoclone. In this particular experiment longevity decreased from a mean of 24 days to 8 days. It will be readily noted from examination of the egg production data that sexual

maturation is accelerated as longevity decreases. Another pertinent observation is the fact that the acceleration of growth is followed by a decrease in maximal size of the animal.

Again, as illustrated in figure 6, the young orthoclone appears to yield diametrically opposed results. As longevity is increased the growth rate is decreased but maximal size is in excess of the parental stock.

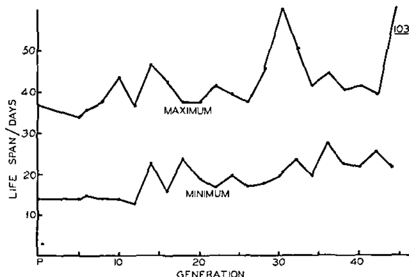


Fig. 3. Maximal and minimal life spans in a young orthoclone carried through 49 generations.

Several points may be derived from these experiments:

1) Age of the mother conditions longevity of the offspring.
2) The ageing factor is extra-genic.
3) The ageing factor appears at the time of cessation of growth.
4) Accelerated ageing is accompanied by accelerated growth but decreased maximal size.
5) Retarded ageing is accompanied by retarded growth but increased maximal size.

In view of the fact that an intimate relation exists between rate of growth, *growth regulation and ageing one may postulate a unitary principle* which serves as a common denominator. Whether this is a biochemical process, a substance, or a physical state remains to be determined. It is striking that the experimental observations on the primitive rotifer as well as the conclusions derived therefrom are entirely compatible with conclusions drawn from mammalian experiments (64, 68, 98, 99).

LONGEVITY OF ORTHOCLONE - GENERATIONS

2 4 6 8 10 12 14 16 18

AGE OF ORTHOCLONE - DAYS

FIG. 4. Recapitulation of relation between longevity of orthoclones and age of various orthoclones It will be noted that even the 6 day orthoclone (6 days being the first day of adult life) expresses presence of the ageing factor.

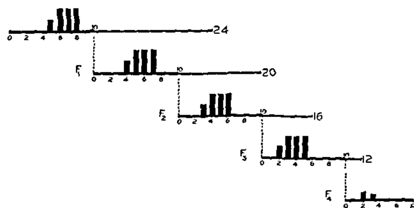


FIG. 5 An old orthoclone carried through 4 generations. Note that the mean life span (expressed in numbers) decreases steadily but that the day on which egg laying begins is progressively shifted to an earlier age.

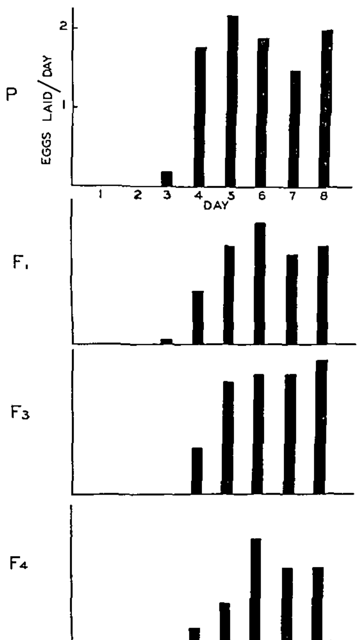


FIG. 6. Similar data as in figure 5 but in a young orthoclone. Here sexual maturation is progressively retarded.

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2

AGEING OF TISSUE FLUIDS

E V COWDRY

St. Louis

Operation of the balancing mechanisms called homeostatic by Cannon, and presented by Shock in Chapter 18, provides constancy within narrow limits in the temperature of the body, sugar content, acid-base equilibrium and other properties of the blood. With ageing these mechanisms become more and more restricted in their ability to maintain this essential stability. Old men and old women adapt themselves less well to many internal and external disturbances. In their bodies and throughout life the blood stream is the central unifying factor. The processes of ageing can be studied to great advantage insofar as they influence these homeostatic mechanisms.

In addition, there is evidence that the cells outside the blood vessels exist in tissue fluid environments which are adjusted to their needs and are not necessarily uniform throughout the body. Cells influence and are influenced by environments and if these fluids are significantly different in different localities and change with age, each in its own way, the problem of ageing involves their close scrutiny in all parts of the body.

Cellular Adjustments

In this chapter only a general view of the most interesting ones can be given.

A protozoan, fixed to the rocks of the stream bed, must hold tight to an inanimate surface and adapt itself to its fluid environment which is the water in the stream. The cells of our bodies are very much more sheltered and they vary with factors not operative in the same way in the external environment. Some of them are presented diagrammatically in figure 1.

A. An epidermal cell of the skin, the cell wall of which is heavily outlined, is protected from the external environment by layer upon layer of

dead cells. It varies with 1) this environment to some extent, 2) other cells next to it and 3) the tissue fluid which exists between it and the blood stream and percolates slowly between it and its living neighbors.

B. An epithelial cell, which lines a lumen connecting with the outside world, is farther removed from the external environment. It is exposed only to those substances of external origin which run the gauntlet of various sphincters, digestive secretions and other protective mechanisms. It varies with 1) the material in the lumen, 2) other cells next to it and 3) the tissue fluid.

C. A connective tissue cell is more deeply placed. It is protected by epithelium from the external environment and the projections into the

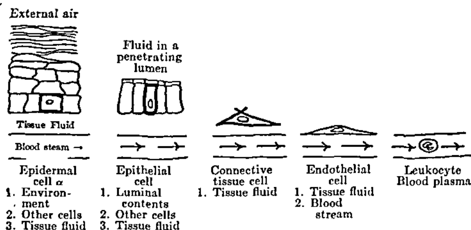


Fig. 1. Diagram showing different kinds of cellular adjustment

body of the above mentioned lumina. It varies with any cells or fibers with which it is in contact and with the tissue fluid which bathes it.

D. A vascular endothelial cell is still more sheltered first by epithelium and second by tissue fluid. It varies with 1) the tissue fluid and 2) the blood stream.

E. A leukocyte in the circulating blood is most sheltered of all since it is protected by epithelium, tissue fluid and endothelium. It varies only with the blood plasma and other blood cells and endothelium with which it comes in contact.

It is evident that the vital adaptations of single-celled creatures in watery surroundings are fundamentally different from the cells which inhabit our bodies.

Estimates of total body water, made by the new technique of measuring the dilution of antipyrine, reported by Steele et al. (1950) show no apparent relationship between age and water content. However the percentage of body weight made up of water is distinctly less in females than in males.

Tissue Fluids Defined

These include all the fluid environments in which cells live within the body except blood and lymph. Note the qualification, "within the body", because fluids within lumina communicating with the external environment of the body are not strictly speaking histologically within the body. To be precise, we mean to exclude those in the alimentary, respiratory, urinary and genital tracts and those in the lumina of all glands discharging into these tracts as well as those in the lumina of all glands discharging onto

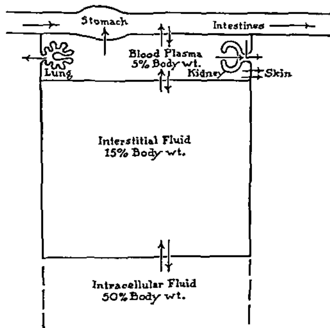


Fig. 2. Proportions of body fluids (after Gamble, 1937). The interstitial fluid includes both tissue fluid and lymph.

the external surface of the body. In these situations the said fluids are within tubular channels, leading more or less directly to the external environment, which channels are everywhere separated by their epithelial linings from the surrounding tissue fluids.

Stated differently, "tissue fluid" is an inclusive term designed to cover all extracellular body fluids except blood and lymph and fluid secretions and excretions poured into lumina connecting with the external environment. Peritoneal fluid is included under this designation, despite the fact that in females it is continuous at the ostia of the Fallopian tubes with the fluid in channels connecting with the outside. Justification for its inclusion is found in its location in males with a closed cavity and in its similarity

in character and in development to pericardial and pleural fluids in both sexes. Tissue fluid includes all the interstitial fluids represented in figure 2, except when these are taken to comprise also lymph. The tissue fluid of the connective tissues is commonly referred to as "ground substance". This term is less satisfactory for the reasons that it implies a single material and does not convey the idea of fluidity—something capable of flowing. Other tissue fluids are known by special names: articular (synovial), cerebrospinal, arachnoidal, perilymph, endolymph, intraocular, and so on.

Obviously tissue fluids vary in amounts in different situations. Where sufficient amounts can be collected for direct analysis they are quite well known to biochemists. When they exist only in microscopic amounts they are usually rather promptly dismissed by biochemists with the statement that all of them are fundamentally transudates from the arterial blood stream and, since the arterial blood plasma going to all parts of the body is of about the same composition, they, also, are probably of uniform composition. But to cellular physiologists this simplification is altogether unjustified.

Among the many features that mark tissue fluids as basically different from blood plasma and lymph is the establishment early in life of local differences in them. They do not circulate under pressure, as blood plasma does. Neither are they pushed forward in one direction, like lymph. There is a feeble and necessary circulation of cerebrospinal, endolymphatic and intraocular fluids; but, in general, tissue fluids are localized. While each maintains its distinctive properties, they are replenished at different rates, depending, as we shall see, on many factors including the degree of vascularity. Unlike blood plasma and lymph, some tissue fluids can accumulate in large quantities, witness edema, ascites, and pleural effusions.

Differential Factors

Tissue fluids exhibit a wide range in properties from a watery through a gel-like consistency to the firmness of cartilage.

Many factors are involved in the creation and maintenance of local tissue fluid environments suited to their cellular inhabitants and to the functions served by these cells plus their environments, for both contribute to the dynamic organization of the body. Some factors are indicated diagrammatically in figure 3. In this an arbitrary area of tissue is represented as enclosed by dotted lines.

Boundaries

Evidently tissue fluids are not all equally enclosed in barriers which restrict fluid movement into them and out of them as implied by the arrows above and to the right in figure 3. Nor is the barrier usually the same

on all sides. Subserosal tissue fluid of the intestinal tract is sandwiched between a thin and highly permeable mesothelial membrane on one side and the tunica muscularis on the other, while it can spread laterally considerable distances. Intestinal subepithelial tissue fluid is stationed between a single layer of epithelium and the tunica muscularis and is without restriction laterally. Synovial tissue fluid is limited by synovial membrane laterally and articular cartilage distally and proximally. These, and other, differences in boundaries are not without influence in conditioning the respective tissue fluids.

Blood supply

The blood, coursing through the area under hydrostatic pressure, contributes to the tissue fluid and also removes some fluid from it through the endothelium of capillaries and venules as is suggested by the long and

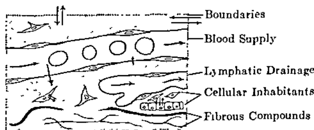


FIG. 3. Schematic representation of factors in regulation of tissue fluids

short arrows. Transfer through endothelium of other segments of the circulation influences the segments involved but has less influence on tissue fluids farther afield. Crystalloids enter and leave easily because of small particle size, whereas colloids of large particle size are usually retained in the blood stream. The former are substances like sodium chloride which on evaporation of solutions yield crystals. The latter when present in fluids on evaporation yield glue-like residues. The term "colloidal" is derived from *kolla*, glue + *eidos*, appearance. But some crystalloids can become colloidal so that the distinction refers more to a condition of material than to a fundamentally different kind of material. The conditioning influence of the blood stream will depend upon its volume and the permeability of the vascular channels. In avascular tissues, such as epidermis, cornea and cartilage, the actual endothelial walls facilitating addition and removal are held at a distance; while in highly vascularized tissue they are immediately involved and to a much greater extent. Increase in permeability, either by injury to the endothelium or by stretching and thinning of the endothelium, will increase the transfer of crystalloids considerably and of colloids to a less extent.

Lymphatic drainage

The lymphatic and venous blood streams are the principal mechanisms of removal. Lymphatic capillary endothelium is more permeable to substances of large particle size than is vascular endothelium so that removal by it is different in quality. The volume of lymph leaving the area also makes a difference. In alymphatic tissues such as bone marrow, brain, epidermis and so on, this factor is minimal as compared with what it is in tissues rich in lymphatic capillaries. The volume of fluid entering an area of tissue fluid through its boundaries, and *via* the blood stream and lymph, is usually equalized with that leaving by the balancing of these factors; for, if it were greater, the tissue would swell; if it were less it would shrink. But some volumetric differences are temporary and of functional value.

Cellular inhabitants

Not all of these have quite the same status. The epithelial ones that limit tissue fluids are of many sorts. The influences exercised by intestinal epithelial cells and by epidermal epithelial cells on their respective tissue fluids can hardly be the same. The displaced epithelial cells that produce internal secretions, which are first poured into their tissue fluid environments, will be referred to later. Deep lying tissue fluids devoid of any epithelial cells, and possessed only of cells of mesenchymal origin, clearly are also likely to differ in the cellular contribution to their makeup. A potentially differential factor, especially in the purely mesenchymal tissue fluids, is the ratio of the volume of living cells to the volume of fluid. Another depends upon the kinds of cellular inhabitants; for they can be of many sorts present in different relative numbers, each relying on the fluid for supplies and contributing to its composition in accordance with its own particular manner of life. Evidence is heaping up that the fibroblasts produce a gel-like polysaccharide material—hyaluronic acid. The same cells are also concerned in the formation of fibers. They, or other cells, are involved in the production of sulphated mucopolysaccharides. Differing amounts of these two kinds of gels create differences in the tissue fluids concerned as do also differences in activity of hyaluronidase and other spreading factors (see Duran-Reynals, 1950).

Fibrous non-living components

The presence in the tissue fluid of non-vital components of different kinds and in different amounts is a factor, or group of factors, difficult to evaluate. A tissue containing cells and pervaded with fibers is different from one containing only cells. The fibers are of at least two different sorts: collagenic and elastic. Tissue fluids may differ in the relative proportions of these fibers. The fibers may obstruct the flow of fluid when they are

densely matted together. In certain situations as in the walls of arteries, the elastic ones constitute definite membranes (membrana elastica interna, for instance). Since the two kinds of fibers are of different composition, physical adsorption of substances in the fluid on their surfaces is unlikely to be the same. Consequently, adsorption, with perhaps later incorporation into the substance of the fibers of materials in the tissue fluid, could well operate as differential factors in the case of two tissue fluids not possessed of equality in amounts and kinds of fibers. Calcium accumulates in the tissue fluid at the surfaces of elastic fibers in arterial walls. With increase in age from the decade 11–20 to the decade 71–80 the percentage of calcium in dry elastin increases from 0.4 to 6.9 (Lansing, et al., 1950, 1951). The taking in of calcium by elastic fibers is consequential. The alterations in the amino acid content of elastin with advancing age, reported by the same investigators, are also significant in this connection: aspartic from 0.14 to 1.5 per cent and glutamic from 1.6 to 4.4 per cent. It would appear that the tissue fluid in these arteries is not identical in composition with that of other mesenchymatous tissues in which such chemical alterations do not take place. Differing proportions of the collagenic fibers are likely to act as differential factors in their own tissue fluid environments. Reticular fibers seem to differ from collagenic ones more in their characteristic location, fine caliber and net-like arrangement than in their chemical composition. Nevertheless their abundance, or their rarity, in tissue fluids would constitute factors at least potentially differential.

Following cell death the composition of the tissue fluid changes. Bunting (1950) calls attention to the material staining blue with hematoxylin in sections of areas showing necrosis. This property is in his opinion consistent with the presence of desoxyribonucleic acids and associated histones derived from nuclei of necrotic cells of the exudate and the parenchyma. Amounts of these substances so small as to escape notice may be liberated in tissue fluids in consequence of nuclear disintegration—an occurrence more extensive in some tissues than in others. If there is a marked differential in cytoplasmic breakdown as between two tissues it is to be anticipated that this would tend to produce diversity in composition of their tissue fluids minimized of course by speed in draining off of the products.

Clearly the number of possibly differential factors is almost endless. The maintenance of tissue fluids at different temperatures is another. In this connection a paper by Bazett and McGlone (1927) on temperature gradients in human tissues should be consulted. The experiments of Huggins and associates on bone marrow will be mentioned later. That the testicle cannot operate at abdominal temperature is well known. The corneal temperature is very low.

Classification of Tissue Fluids

The properties of individual tissue fluids, influenced by these five groups of factors, are of importance to us for it is in these fluid environments that cells live, multiply, transact their business, age and die. It is also in these locations that some of them embark on malignant antisocial careers. Almost all the cells live in such environments, or are affected by them; since they stand between them and the external environment or between them and the blood or lymphatic streams, all living cells are aquatic. We shall simply try to visualize the chemical and physical properties of the fluids in which the cells live, the kind and degree of protection which they have from the external environment of the body, their relation to fluid streams within the body (to possible carcinogens) and some of the alterations they undergo with advancing years.

Tissue fluids from these standpoints are divisible for convenience into three large groups; 1) Those which are *subepithelial* in position protected only from the external environment by epithelium and from the blood by endothelium. 2) Those which are more deeply situated within *mesenchymal* tissues remote from the environment and separated from the blood stream by endothelium which carries to them many chemical substances both of direct internal origin and more remotely of external origin. 3) Those which are *protected* from agents of external origin by their position, or from agents of internal origin by cellular membranes additional to vascular endothelium.

Subepithelial tissue fluids

These are separated from the blood stream by vascular endothelium only and are said therefore to be of the first order.

Consider first the fluid environments of the epithelial cells stomach to rectum inclusive. They constitute only a single layer but their relations are not as simple as is indicated in the diagram (fig. 4). To begin with the cells are of several varieties. Those that absorb fluids from the lumen are chemically more exposed than those that discharge fluids into the lumen. And the cells that face the lumen directly are more exposed both to chemical and mechanical injury than are those situated farther away from the lumen lining tubules in which the direction of flow is mainly or wholly toward the lumen. There are, moreover, marked differences in exposure in various parts of the tract depending on the character of the mixture of substances in the fluid within the lumen. Some of the substances have run the gauntlet of selective nervous mechanisms operating at higher levels and have not been regurgitated from the stomach, while others have been poured into the lumen from glandular appendages such as the liver.

Protection is given by mucous sheets, by the yielding character of the walls of the tract and by reflex modifications in mobility.

The proximal surfaces of gastrointestinal epithelial cells are bathed in tissue fluid of the first order as is represented crudely by stipple in figure 4 Indeed, they may almost be said to float on this fluid loosely anchored by a few elastic and collagenic fibers which are not indicated in the figure. Contributions to this subepithelial tissue fluid through vascular endothelium, and especially through the epithelial sheet itself from the contents of the intestinal lumen, are indicated by arrows. Those from within (arterial blood) are uniform in quality in the different segments of the tract, whereas those from without (intestinal lumen) are, as already intimated, of very diverse properties. Exit of fluid is mainly by blood vessels, lymphatics and by passage in the reverse direction out through the epithelial sheet into the intestinal lumen.

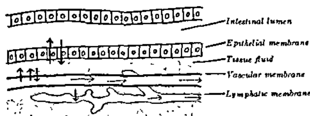


FIG. 4. Subepithelial tissue fluid. This also is one of the first order indicated in light stipple.

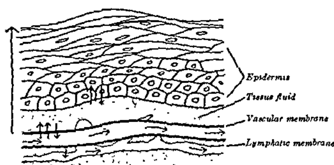
To attempt, even in a halting way, to enumerate all the fluid shifts would consume altogether too much space. Suffice it to say that the cellular inhabitants stand in what may be called the fluid crossroads of the body. The changes in traffic as age advances have an important bearing on the whole body. They are basic to the excellent description of the Digestive System given in Chapter 20.

Judging from reported deaths from cancer in different tissues the cancer hazards are here greater than elsewhere. In 1948 deaths from cancer of the stomach were more numerous than from cancer in any other organ. One is tempted to think that the fluid within the lumen is primarily responsible in bringing carcinogens to the epithelial cells and that these agents are taken in by mouth. Difference in dietary habits seems to be largely responsible for the fact that 16 per cent of all deaths reported from cancer in the United States are from gastric cancers while in Indonesians the percentage is only about one.

An instructive contrast is afforded by the fluid environment of epithelial cells of the epidermis (fig. 5). Distally they are in contact, not with water, but with air and are therefore dead. No cells can live exposed directly to

air. The corneal cells of the eye and epithelial cells throughout the length of the respiratory tract are protected from air by thin films of fluid. However, the distal surface of the epidermis is kept pliable and in good condition by the oily secretions of sebaceous glands and the dead cells at the surface shield the living ones beneath. Exposure of the latter to waterborne injurious substances is consequently less and different in kind from that of intestinal epithelial cells. Obviously exposure to mechanical, thermal and radiation injuries is greater.

Proximally the innermost of these epidermal cells are in direct contact, like the intestinal ones, with a tissue fluid of the first order with blood and lymphatic capillaries playing a similar role, minus repeated inundations



[illegible] of dermal tissue fluid represented in light stipple

by fluids entering through the epithelium from without. Both epithelial and mesenchymal tissues likewise here are involved in determination of the character of these tissue fluids.

Living conditions for citizen cells within them are not to be regarded as identical though there is a basic similarity. The thickness of the epidermal sheet and greater exposure to the external environment in parts of the body not protected by clothing are to be reckoned among others as differential factors. Age changes are many and varied. They include re-

and hair and in responsiveness to carcinogens. See Chapter 29, Cowdry and Andrew, 1950; Cowdry and Suntzeff, 1944; Cowdry, Carruthers and Suntzeff, 1948.

The relative infrequency of deaths from skin cancer is not a reliable

measure either of the exposure of the cells to carcinogens or of their susceptibility to them. This is because skin cancers are easily seen, and are usually promptly destroyed in one way or another. If this were not so it is safe to predict that the deaths from skin cancer would surpass in number the deaths from gastric cancer.

Brief further reference to the fluid environment of epithelial cells constituting the optic corneas is worthwhile. The cornea in common with the epidermis is a many layered epithelium of ectodermal origin. But it is translucent—bathed externally by a watery saline fluid, not by oily sebum, backed by a tissue fluid of the first order from which blood and lymphatic capillaries are held at a distance, which, because of its avascularity and evaporation of water at this corneal surface is maintained at a lower temperature (see Ida Mann, 1932, and Chapter 9). Exposure of these

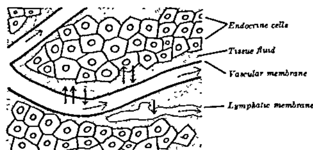


FIG. 6. Endocrine tissue fluid

epithelial cells to carcinogens is therefore unique in several respects and cancer is of rare occurrence.

The secretory cells of many endocrines are of epithelial origin, having lost their connection with internal surfaces in the course of development. Their tissue fluid environment lies deeply in the body, shielded from the direct action of external carcinogens. These environments are conditioned by the blood stream, the lymphatic drainage, the activities of the secretory cells themselves and to a lesser degree by associated connective tissue cells and fibers not shown in the diagram (fig. 6). Such internal secreting cells seem to be immune to the hormones they produce though it is reasonable to expect that the concentration of the said hormones is greater in their own limited tissue fluid environments than it is after distribution through the blood stream to much larger areas. The waning of activity on the part of the secretory cells as age progresses is for experts to discuss (Chapters 15–17).

Deep-lying mesenchymatous tissue fluids

These cellular environments are likewise of the first order since they are separated from the blood stream only by vascular endothelium. In the mucosal, subepidermal and corneal tissue fluids mesodermal components of course play an important part. It is admitted that our classification of tissue fluids is not into sharply defined categories. We include under this heading the tissue fluids in the control of which epithelium is not closely involved.

Some of these are rather ill-defined anatomically and stretch for considerable distances. Blood vessels, lymphatics and nerves usually course in *loose connective tissue* and there is a tendency for fluids within it to spread alongside of these structures. The spread is more definitely directional when these are confined in more or less distinct canals, such as the inguinal, the femoral and the portal canals. The chances of spread are also restricted in the loose connective tissue between muscles which can easily be separated and contract independently so that their surfaces slide over each other.

Among deep lying mesenchymatous tissue fluids, which are more localized, that of *dentin* is developmentally most closely related to our first group of subepithelial tissue fluids. Its relationships are represented in figure 7. Distal protection is given not by a layer of living epithelium, but by dead dental enamel, an epithelial product and the hardest tissue in the body. No living epithelial cells are resident in dentinal tissue fluid nor contribute to its formation. However, some diffusion from the oral cavity through the enamel into it must be reckoned with, likewise variations in temperature mainly from drinking ice cold or almost boiling hot liquids. Dentin itself is avascular. Fluid seeps into it from the underlying dental pulp where its principal source is the blood stream. See the two arrows pointing upward in figure 7. Some fluid passes back through the vascular endothelial membrane and some enters the lymphatics. A single layer of elongated mesodermal cells (odontoblasts) is placed in the pulp next to the dentin. Their nucleated cell bodies are in the pulp and each one of them extends a long process into the dentin which may reach a distance as far as 2 mm. to the dento-enamel junction where it branches profusely. These processes are contained in dentinal tubules the nature of the walls of which is not definitely known. The tissue fluid of the pulp seeps into the dentin through the dentinal tubules along the surfaces of the processes of the odontoblasts contained within them. Particles of India ink injected into the pulp move in this direction (Fish, 1932).

This tissue fluid, within the dentinal canals, is but a small fraction of the total tissue fluid in the dentin. Noyes (1929) has calculated that the

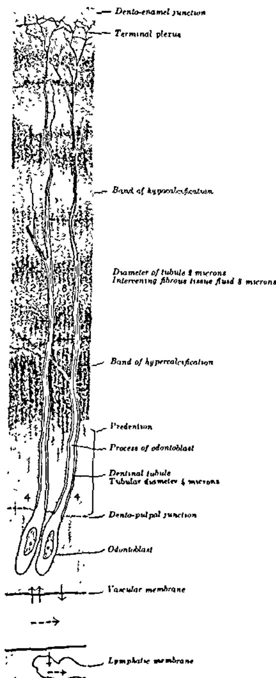


Fig. 7. Di[illegible] of two odontoblasts in dental pulp extending [illegible]

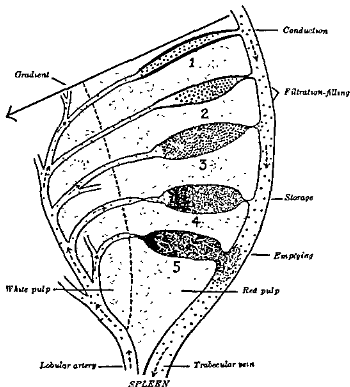
average diameter of a dentinal tubule is 2 microns and that they are separated by 8 microns of ground substance. This ground substance is fibrous and in it calcium salts are accumulated much as in bone. They can be withdrawn, but not with the same facility as from bony tissue fluid. They are concentrated in irregular bands of hypercalcification separated by bands of hypocalcification, but the dentin next the pulp contains less calcium than that farther removed from it and is termed predentin. Consequently there is a vertical gradient of increasing calcification in the tissue fluid passing away from the vascularized pulp. The successive bands of calcification laid down rhythmically in the rat's incisor (Schour and Steadman, 1935) are really a series of vertical gradients one on top of the other.

The shift of fluid in human dentin is not altogether through the dentinal tubules, out of them at right angles into the fluid matrix and back again; for some of it may enter the superposed enamel or the cementum, which latter limits the dentin laterally and affords attachment for fibers that hold the tooth in place. Conversely, a little fluid may move into the dentin from the enamel and rather more from the cementum. The passage of tissue fluid comparatively long distances through these myriads of extremely fine tubules possessed of living cores, in which there are currents of fluid, gives abundant opportunity for surface action and adsorption. Moreover the conditions are not altogether static; because, in addition to the vitality of the cytoplasmic processes of the odontoblasts, the dentin itself is slightly elastic since it provides an effective yielding backing for the crown of enamel. Slight alterations in the length of hundreds of thousands of dentinal tubules will cause agitation of fluid in them as well as in the tissue fluid around them.

Of all the tissue fluids in our bodies that of the *spleen* is perhaps the most interesting in the light of investigations by Knisely (1936). He has managed to observe directly in the spleens of living animals contributions being made to the splenic tissue fluid by the venous sinuses. The spleen is divisible into thousands of lobules and the structural relations at the side of one nodule are illustrated diagrammatically in figure 8 with many details omitted. The white pulp is on the left. It is separated by a broken line from the red pulp on the right. The course of the blood stream is indicated by arrows. The venous sinuses are sausage-shaped bodies in the red pulp. Stages in their cyclic activity are represented from above downward in figure 8.

In the *first* (1), called conduction, blood flows through quickly and the wall is thick and consequently not very permeable. In the *second* (2, 3), known as filtration-filling, the efferent sphincter, which guards the opening into the trabecular vein, closes. The sinus gradually fills, the wall thins, plasma filters into the surrounding tissue fluid and the cells become more

closely packed together. In the *third* (4), the afferent sphincter closes, prevents more blood from entering and the stage is termed storage. After an interval the *fourth* phase of emptying begins by opening of the efferent sphincter. The cheesy mass of blood cells breaks up, the afferent sphincter



opens and the contents are flushed into the trabecular vein. Then the cycle begins again with free conduction of blood through the sinus.

This is a situation in which almost all of the plasma filters into the tissue fluid, but it is possible that some substances remain adsorbed on the surfaces of the blood cells. Since the filtration is mainly in the red pulp, and the capillaries in the white pulp show no signs of being as permeable as the venous sinuses, it follows that a gradient in composition of the tissue fluid is probably established. This extends from the region where the plasma contribution is largest to where it is least as suggested by the large solid arrow at the top of the figure. Another factor likely to produce such a

gradient is the difference, both qualitative and quantitative, in the cell content of red and white pulp and the resultant differences in metabolic requirement. The tissue fluid is shifted by passive and rhythmic contractions of the whole spleen.

It cannot therefore be doubted that the cells of the spleen enjoy a tissue fluid environment all their own in which it is to be observed that there are no epithelial elements. The presence of so much plasma protein, which diffuses into the white pulp in the direction of the gradient, may contribute to the hyaline infiltration of the arterioles in the white pulp, which is a *conspicuous feature of ageing of the spleen. It is however not the sole* cause, for similar infiltration occurs in a less marked degree in other organs.

In contrast to that of the spleen, the tissue fluid of *vascular walls* is scanty and there are no similar arrangements to filter off blood plasma into it. In arteries the blood stream is a source of oxygen-rich tissue fluid and some tissue fluid may pass in the reverse direction out into the arterial lumina. This is represented by the uppermost arrows in figure 9. This fluid permeates through the meshes of the internal elastic membrane and penetrates into the media. On the opposite side fluid enters from the vasa vasorum and leaves by the same vessels plus adventitial lymphatics. In the substance of the wall are densely packed smooth muscle cells, fibroblasts, elastic and collagenic fibers disposed mostly circularly about the lumen. Between these structural components the spaces originally occupied by tissue fluid seem rather inconspicuous when viewed microscopically in stained sections of affixed tissue, owing to the contraction of muscle and to shrinkage. It contains the polysaccharides already mentioned and a good deal of calcium salts. The amount of tissue fluid *in vivo* is probably here, and in other locations, 10–20 per cent greater than one would judge from such appearances, and there is a rhythmic and effective shifting of this fluid over the structural components as the arteries pulsate. Many arteries are highly individualistic in their structure and differences in their tissue fluids are to be expected. Accurate measurements of their metabolism (Kirk, 1951) open up a new line of investigation.

In veins hydrostatic pressure of the blood stream is much less and oxygen containing fluid contributions from the lumina are lacking. The vasa vasorum may discharge even into the venous blood stream. It is safe to say that their tissue fluid is less rich in calcium, the adsorption of which on elastic fibers is not promoted by pulsation of the venous walls. Although the content of venous blood is much more diversified, because it comes from different areas, the tissue fluids of veins are more uniform in composition than those of arteries.

Age changes in arteries (Chapters 13–14) are of greater consequence than in any other tissue in the production of chronic invalidism. A survey

by the U. S. Public Health Service places modifications in the cardiovascular system as second only to those in the nervous system in this regard. Since many degenerative changes in the nervous system are of vascular origin the blood vessels come first by a wide margin.

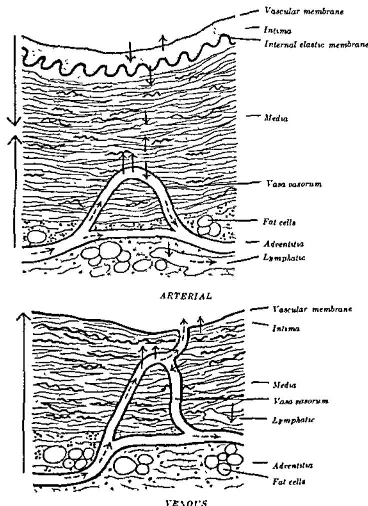


FIG 9. Vascular tissue fluids In the arterial wall oxygenated tissue fluid comes both from the lumen and periphery, in the vein only from the periphery The large arrows at the side show directions of gradients.

Malignant transformation of cells in vascular walls of both sorts is a rare occurrence even at ages when it is at its height in epithelia. Some other mesenchymatous tissue fluids are represented diagrammatically in figure 10.

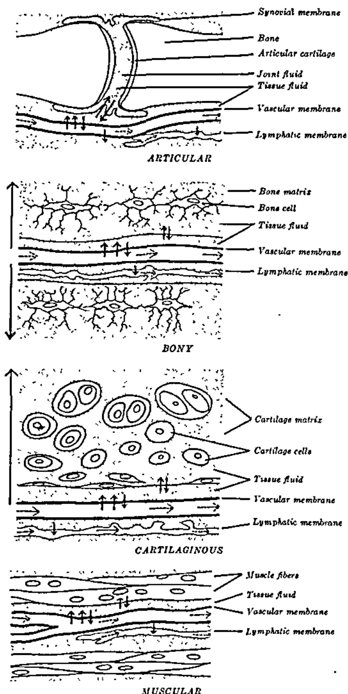


Fig. 10. Other deep lying mesenchymatous tissue fluids

MUSCULAR TISSUE FLUID lies between the muscle fibers. It contains, in common with all fluids of this large category, connective tissue cells and fibers not shown in the diagrams. Bundles of fibers are partitioned off by sheaths of connective tissue (perimysium) and the muscles are invested in sheaths of connective tissue (epimysium). Flow of fluid is parallel to the length of the fibers. Fluid enters and leaves through vascular endothelium. Some of it also leaves *via* lymphatic capillaries, but in skeletal muscle there are few if any lymphatics.

BONY TISSUE FLUID is like many others of unknown composition, but the environment of the fluid and the entrance and the exit from it are interesting. As they differentiate bone cells extend many fine cytoplasmic processes into the tissue fluid about them and the processes of neighboring cells coalesce. These processes are later somewhat withdrawn; but the spaces that they originally occupied remain and constitute a canalicular system filled with tissue fluid. This fluid bathes the cell membrane and its blunted processes and is continuous from cell to cell. We recall how the delicate processes of odontoblasts are bathed by fluid within the dentinal tubules. The surface of separation between the fluid in the canaliculi and the remainder of the tissue fluid, which has become solidified, is sharply defined but its actual make-up remains to be determined. So there are here two tissue fluids, one fluid and one solid but permeable. The two are so intimately connected that they cannot be separated for chemical analysis. Neither can their relative volumes be accurately determined according to Huggins (1937). "Many if not all substances present in the body fluids and difficultly soluble in a faintly alkaline aqueous medium are deposited in new bone." The composition of bone of different ages will be to some extent different depending upon the availability of substances in the circulation at the time that it is formed. Without specifying the age, but presumably for both old and young bone of adults, Maximow and Bloom (1934) say that the interstitial substance (our tissue fluid), which includes everything but cells, contains 30–40 per cent of organic material (chiefly collagen, called ossein, plus small amounts of osseo-mucoid and osseo-albuminoid) and 60–70 per cent of inorganic material of which the calcium exists in the form of dahlite. However, in advanced years there is a decrease in calcium so marked as to be easily noticed in x-ray photos.

The movement of calcium out of bony tissue fluid and into that of arterial walls appears to take place at about the same age level. It is a remarkable phenomenon. Cells living out their individual lives in bony tissue fluid, and others in the periosteum that limits this fluid, do on occasion become malignant. The only way that chemical carcinogens can reach their tissue fluid environments is by the blood stream. Mechanical injury to the bones could be a factor in the local traumatic liberation of sub-

stances that might be carcinogenic. On the other hand, the mesenchymatous cells within arterial walls very seldom undergo a malignant transformation. Entry to bony tissue fluid (fig. 10) involves 1) passage out through the wall of a blood vessel into an endosteum-lined space, 2) passage through this lining into the solid tissue fluid, 3) entry into the canaliculi and spread over surfaces of bone cells, 4) giving up of oxygen and nutriment to the cells and receipt from the cells of metabolites, 5) passage in the reverse direction and 6) evacuation by blood and lymphatic streams coursing within the bone to the outside.

The tissue fluids of *bone marrow* afford an instructive contrast to the vascular and splenic ones. They are within rigid walls and are not shifted rhythmically back and forth over similarly adsorptive fibrous filters: neither are they in a soft organ the volume of which changes in the manner related. Alterations in volume take place gradually by operation of factors reviewed by Drinker and associates (1922). Like all tissue fluids they are based on the blood stream. Their separation from the blood stream is peculiar. In these localities blood flows through what Maximow and Bloom (1934) call venous sinusoids which are limited, they say, not by endothelium but by "littoral cells of the macrophage system" through which pass out from the tissue fluid into the blood stream not only granular leucocytes but also non-motile red blood cells by a mechanism "probably regulated by changes in the permeability of the walls of the vessels and in the surface energy." The possibility is therefore created of a difference between these bone marrow tissue fluids and other tissue fluids limited by the usual endothelial membrane.

Bone marrow itself is not of uniform properties. There exist two main kinds, red and yellow. The red variety is a blood cell producer and the yellow is loaded with swollen fat cells. It can be safely assumed that the metabolic rate is higher in richly cellular red than in yellow marrow. Huggins, Blocksom and Noonan (1936) have discovered that in mammals there is a temperature gradient extending from centrally placed marrow to distal marrow, near the ends of the extremities, where it is 4 to 8°C. lower. Huggins and Blocksom (1936) observed that the red marrow decreases in amount and the yellow increases in passing from deep to peripheral tissues. They performed numerous experiments such as bending rats' tails and inserting them into abdominal cavities, thus increasing the temperature, and found that red marrow was increased in amount by elevation of temperature. Evidently the tissue fluid environment of developing blood cells must be maintained at a high temperature just as that of the testicle, which we shall describe later, must be held at a low temperature in order to produce sperms.

Because of these differences in cell and fat contents, in rate of metabolism

and in temperature we would not look for uniformity in hydrogen ion concentration and in composition of tissue fluids of red and yellow marrow. More data are needed. A definite age change is replacement of red by yellow marrow. Sometimes the latter assumes a gelatinous consistency as a result of wasting diseases—a phenomenon which should be sought in very old people.

CARTILAGINOUS TISSUE FLUID is similarly divisible into two parts: the thin fluid within the lacunae in which the cartilage cells are lodged, and the firm but yielding tissue fluid supported by fibers, basophilic polysaccharides and calcium salts and other substances which in turn invests the lacunae. To enumerate the components of any tissue without including "other substances" is in fact an artificial simplification especially in these days when it is becoming clear that trace substances can be very important. Entry (fig. 10) involves 1) passage out through the wall of a blood vessel, which in contrast with the situation in bone, does not itself enter cartilage for cartilage is avascular, 2) passage into the cartilage through a thin layer of mesenchymatous cells and fibers styled perichondrium; 3) slow diffusion through the firm variety of tissue fluid; 4) entry into the lacunae and spread over the surfaces of the cartilage cells; 5) passage in the reverse direction out of the cartilage and evacuation by blood and lymph. On the whole, the cartilage cells are more protected than the bone cells.

ARTICULAR FLUIDS are called synovial because they have the consistency of slippery white of egg. The word is derived from the Greek *syn*, together, and the Latin *ovum*, an egg. They contain mucin. Meyer, Smyth and Dawson (1938) have reported in bovine synovial tissue fluid "... a sulfur- and phosphorus-free polysaccharide acid of high molecular weight, containing per equivalent weight one equivalent each of nitrogen, hexosamine, acetyl and hexuronic acid." It is not bound to protein but occurs as a salt. There is no reason to think that human articular fluid is radically different in composition. Since the work of these investigators our horizon has broadened. There is no distinct membrane separating articular fluid from the tissue fluid of the articular cartilages and for this reason it has been classified as a tissue fluid of the first order. But most of the entering fluid passes through the synovial membrane from the tissue fluid outside before entering. This is a more valid reason for classifying articular fluid as a tissue fluid of the second order.

Membrane-protected tissue fluids

These are called tissue fluids of the second order because they are separated from those of the first order by membranes (fig. 11).

PERITONEAL FLUID (dense stipple) is a tissue fluid of the second order because it is separated from perivascular tissue fluid of the first order by

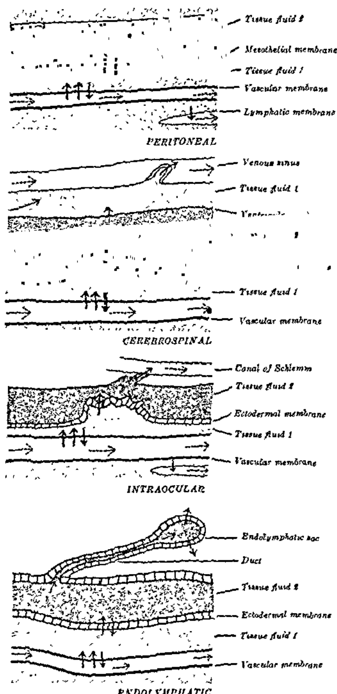


FIG. 11. Membrane protected tissue fluids

a mesothelial membrane. The general direction of flow is out from the vascular lumen into *tissue fluid 1* in which there are, of course, cells and fibers of mesenchymatous origin, though these are not represented. It is then through the thin mesothelial membrane into the peritoneal cavity where it joins *tissue fluid 2*. The return route is the same including however partial evacuation via lymphatics. *Pericardial, pleural* and *scrotal fluids* are of the same general type.

There is a more recognizable circulation in the case of three other tissue fluids.

Cerebrospinal Fluid receives fluid of vascular origin *via tissue fluid 1* through folded ectodermal membranes (the chorioid plexuses). The concentrations of diffusible organic solutes are regularly less than in blood serum (Peters, 1935). A search for data on ageing of the mechanisms involved in stabilization of the cerebrospinal fluid is disappointing. The last word on this important tissue fluid is contained in a book by Merritt and Fremont-Smith (1937). There are almost no changes in the cerebrospinal fluid associated with senescence. The volume of the fluid is smallest in infancy and increases as one grows from adulthood into old age. This parallels the shrinkage in the volume of the brain. Whether there is a steady increase in fluid volume during adult life, or whether there is a flat plateau during this stage, there are no data. Excepting in the cadaver, measurements of volume are quite rough. The cerebrospinal fluid pressure increases from a range of 15 to 80 mm. of water in the new-born to a range of 70 to 180 in adult life. Adult pressure seems to have been reached, however, at six to eight years of age, and we have no evidence of increase thereafter. The vast majority of normal pressures lie between 100 and 160 mm. with the mean in the neighborhood of 140 to 150. It is extremely difficult to get data in aged individuals who are known to be normal. However, the findings of Merritt and Fremont-Smith in 277 cases of cerebral arteriosclerosis are of interest since this group includes a large number of old people. The cells were normal in 85 per cent, the pressure normal in 81 per cent, the protein normal in 75 per cent and the colloidal gold reaction normal in 80 per cent. Normal values for sugar and chloride were also obtained in relatively few cases. Apparently there is no progressive change in these constituents with age. Fremont-Smith went over the records of the Massachusetts General Hospital with special reference to the protein content of the fluid with regard to age, and found that the majority of fluids in patients of 70 years of age and over had entirely normal protein values as compared with young adults (personal communication). Exit of cerebrospinal fluid is chiefly in locations where these membranes are thinner as through the roof of the fourth ventricle into the subarachnoid space where it joins other perivascular *tissue fluid 1*. Thereafter this fluid

enters the venous stream by arachnoidal villi since there is no lymphatic drainage. A villus is indicated as projecting into a venous sinus in figure 11.

Endolymphatic Fluid is formed by transfer of *tissue fluid 1* through an ectodermal membrane but this membrane shows no regional differentiations resembling chorioid plexuses. Some of this endolymphatic fluid may seep back into *tissue fluid 1*; which in this situation is called perilymph. Also, a slow movement of endolymph has been claimed and denied toward the endolymphatic duct and out to the sac through the wall of which it passes out into *tissue fluid 1*.

Intraocular Fluid is likewise a tissue fluid of the second order formed by transfer of *tissue fluid 1* through the folded epithelium of ectodermal origin covering the ciliary process. Like all *tissue fluids 2* it is free from mesenchymal derivatives such as fibroblasts and fibers. Intraocular fluid passing through this membrane enters the posterior chamber and flows between the iris and the lens into the anterior chamber. From the sulcus circularis it leaves by the endothelium lined spaces of Fontana and in some way discharges by the Canals of Schlemm into the venous blood stream. Glucose, urea and other diffusible organic solutes are regularly present in concentrations less than in blood serum (Peters, 1935). But the concentration of lactic acid is greater than in blood serum (Wittgenstein and Gadertz, 1926; Fischer, 1934). According to Davson and Quilliam (1940) "there is a great deal of evidence that the aqueous humor is a filtrate from the blood plasma, molecules of the size of serum albumen or larger being retained while crystalloids are distributed between the two fluids in a manner characteristic of ultrafiltrates in vivo." They have referred to a "barrier" between blood and aqueous humor. In the opinion of Saphir, Appel and Strauss (1941) "it is conceivable that this 'barrier' is capable of preventing the passage of antibodies from the blood plasma to the aqueous fluids thus allowing tumor transplants to grow in this fluid when all other tissues are resistant to their growth"—an assumption which is compatible with the results of earlier work by Becht and Greer (1910) and by Hektoen and Carlson (1910). They worked with the Brown-Pearce carcinoma of rabbits. For us an intriguing feature of intraocular tissue fluid is the fact first demonstrated by Greene (1938) that human cancerous tissue can be made to grow in the intraocular tissue fluids of several animals commonly employed for experimental purposes in the laboratory despite failure of similar transplants in other parts of the body. This can only mean that substances so wide-spread in body fluids antagonistic to the cells of other species are absent, or present in ineffective concentrations, in intraocular tissue fluid. For technical reasons transplantation of this kind has not been attempted in endolymphatic fluid, which in development resembles intraocular fluid rather closely. The related problem of

the metastatic growth of malignant cells in tissue fluid environments, other than those in which they originate, is fascinating.

Summary

The vast majority of body cells inhabit extravascular tissue fluids. The remaining small minority stand between these fluids and blood, lymph or fluids contained in tubes, tubules and alveoli of the alimentary, respiratory, genital and urinary tracts communicating with the external environment.

Tissue fluids are divisible into three groups. *Subepithelial tissue fluids* are in more or less close association with the fluids in the above mentioned tracts or in their glandular appendages. *Deep lying mesenchymatous tissue fluids* are like the subepithelial ones of the first order inasmuch as they are separated from the blood and lymph only by an endothelial barrier but they contain no epithelium. *Membrane-protected tissue fluids* are regarded as belonging to a second order. They are separated from tissue fluids of the first order by thin membranes composed either of mesothelial cells or of epithelial cells of ectodermal derivation.

Only a few of the many tissue fluids have been subjected to direct chemical analysis because of the difficulties encountered in collecting adequate amounts to work with. Others can be characterized by microchemical reactions that bring out differences detectable microscopically. Examination of the boundaries, blood supply, lymphatic drainage, cellular inhabitants and fibrous non-living components of areas of tissue brings to light so many individual peculiarities that the existence of chemical differences not yet discovered in tissue fluids is suspected. Some are watery, others gel-like and still others of very firm consistency. Some are replenished quickly, others slowly. Some occupy situations rather exposed to the external environment, while others occupy very secluded positions.

A fair degree of stability is maintained in all of these otherwise heterogeneous tissue fluid environments. The maintenance of like states in the blood stream is called by Cannon "homeostasis". It is proper to designate the preservation of sufficiently constant conditions of cell life in these many different tissue fluid environments "heterostasis". Alterations can be detected in some of these fluid environments of cells with advancing years. Also the frequency of the malignant transformation of the cells living in them increases and in some of them later declines.

Exposure to carcinogens of cells residing in all tissue fluids is by no means equal. The largest recorded number of deaths in 1918 from cancer and other malignant tumors in particular sites was 26,215 in the stomach. The epithelial cells of this organ are very much exposed to materials taken in by mouth. They are also exposed to substances able to enter their tissue fluid environments of the first order from the blood stream. Deaths re-

corded from cancer of the skin amounted to only 3,508. This does not signify that epithelial cells of the epidermis are less subject to the malignant transformation because the curability of skin cancer is much greater than that of gastric cancer. The kind of exposure from the external environment is different though that from the blood stream is somewhat similar. Reviewing the tissue fluid environments, the exposure to external and internal carcinogens is not identical for any two of them. Another potent factor besides those afflicting the cells through their diverse fluid surroundings, *for all living cells are aquatic, is the kind of lives they lead* which is a function of heredity plus fluid environment. What is important is that the heterostatic mechanisms change with age.

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3

AGEING OF INDIVIDUAL CELLS

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St Louis

Age changes in a cell, as in the body, are the alterations that take place in its individual life with time. To assemble what is known of the age changes in individual cells of the body is obviously a colossal task. Billions upon billions of cells are involved which belong to a great many types—a hundred or more. For the cells of each type, knowledge of structure and function throughout their lives would be necessary in order to recognize alterations with time. Moreover the cellular population changes during the life of the body, some types more frequently than others, and it cannot be assumed that individual cells of the same sort age in the same way in youth, maturity and old age. There is also the difficulty, emphasized in several chapters of this book, of distinguishing uncomplicated or normal ageing from alterations caused by injury and disease. To do this is more difficult for individual cells than for systems or organs because the injury may be of microscopic size, of short duration and leave its mark only in a few cells living at the time, finally to be erased entirely by the appearance of other generations of cells. The following account is presented in the belief that this complex problem can be somewhat clarified if it is considered in relation to a classification of cells in four groups depending upon the character of the lives that they live.

Kinds of Cell Life

If we examine the epidermis we find a layer of cells next to its basement membrane and near the underlying blood vessels. These are called basal cells. As they multiply by mitosis their number next the basement membrane does not increase but some cells are displaced from this privileged position and are shifted nearer to the surface. Those remaining carry on the stream of life, while those more or less continuously displaced

progressively differentiate and renew the epidermis from within to compensate for the loss of dead cells from without.

Individual life begins for a basal cell with its separation from the other daughter cell after mitosis, when it possesses a limiting cell membrane all its own and is in fact an organic individual living or dying as a unit, and extends to the point where its own individuality ceases at the moment when it, in turn, following mitosis, is divided into two other individual daughter cells.

Speaking generally, without particular reference to the epidermis, at the moment of their formation two daughter cells may be similar or dissimilar. This will depend upon the kind of mitosis that has taken place. If it was "nondifferential" the contents of the parent cell will have been equally divided between them. If, on the other hand, it was "differential" a difference will have been established between them owing to unequal partition and both will differ somewhat from the parent cell. The words "nondifferential" and "differential" are here used in the sense employed by Conklin (1924).

After separation each daughter cell must adjust itself to its environment. Since both cannot occupy precisely the same position the influence of environment will also tend to be differential. A slight advantage in nearness to the blood stream may be consequential. This positional factor is obviously of great importance in respect to the daughter epidermal cells that retain a basal location. Such basal cells are comparatively undifferentiated and may be called *vegetative intermitotics*. They constitute a source of new life one cell thick that encases the body. But while their main function is reproductive, it would be unsafe to assume that they are not useful in other ways.

Red bone marrow is also a producer of cells. The cells that live undifferentiated intermitotic lives in it are less easily identified. Some claim that they are capillary endothelial cells. Others think that they are extravascular. But the fact remains that, like the basal cells of the epidermis, they are stationed very close to the blood stream. Though some products of their mitotic divisions go on to produce blood cells, a sufficient number continue as long as life of the body lasts in an undifferentiated state, segregated in masses and protected from mechanical injury by strong bony walls. The spermatogonia of the testicle are also vegetative intermitotics.

The cells that are formed from vegetative intermitotics, and begin to differentiate, may also be intermitotic with lives extending from one mitosis to the next. Their lives are, however, different insofar that they exhibit increasing specialization. Consequently they may be designated *differentiating intermitotics*. Where the epidermis is thick, there may be

several generations of cells of this kind each showing more differentiation in individual lives than the foregoing before cells are produced whose lives are ended by death. A definite number of generations of differentiating intermitotics exist between spermatogonia and spermatozoa. In bone marrow an unknown number of generations of differentiating intermitotics intervene between the vegetative intermitotics and blood cells capable of discharging their special functions but some of them are well marked. Each twin differentiating intermitotic blood cell begins at about the stage of differentiation where its parent ceased to exist as an individual. It accumulates more hemoglobin, or more specific granules, as the case may be, and the cell next in series starts at about where it left off. The lives of such cells are steps toward definite goals—erythrocytes or leukocytes. But it is doubtful whether differentiating intermitotics themselves ever serve the special function which the cell at the end of the series will be equipped to discharge. Often they are not adequately differentiated or suitably placed. Erythroblasts have a good deal of hemoglobin; but, since they usually do not circulate, they cannot normally act as oxygen carriers. In neutrophilic myelocytes the powers of motility and phagocytosis are very rudimentary as compared with those of the corresponding leukocytes. Spermatocytes certainly cannot function like spermatozoa.

The highly specialized cells, formed from the last differentiating intermitotics at the ends of the series, ordinarily live entirely different lives. They are "end cells". Their individual lives begin, as before, after the last mitosis and extend through youth, maturity and old age to death. In a word, they are postmitotics. There are a great many of them. They may be divided into two groups representative of levels in differentiation.

The first we designate *reverting postmitotics*; because, though they generally age and die, some of them are capable of reversion. That is to say, they can halt the ageing process, undergo mitosis and give rise to two other cells capable of functioning as they did. Millions of epithelial liver cells are reverting postmitotics. They are at the height of differentiation for their type; but, when there is need for more liver cells owing to removal or death of a large number of their fellows, they can and do multiply to make good the loss. Those most likely to multiply are chiefly located near the periphery of the lobules and are thus more advantageously placed than the more central liver cells because arterial blood reaches them first. Renal epithelial cells are likewise at the head of their particular ladder as far as differentiation is concerned. They are very seldom seen in mitosis, but some of them can cease temporarily to function and multiply in what is termed compensatory hyperplasia. Thyroid cells are on a similar basis. There is a difference of opinion as to the capability of ciliated cells to divide (see Kindred, 1927), but in frog tadpoles they cer-

tainly do, as Kindred has beautifully illustrated. According to Schafer (1912), goblet cells of the intestine are permanently differentiated. Evidence about them is critically discussed by Macklin (1932). Ordinary capillary endothelial cells (not those of the special capillaries in the bone marrow) are reverting postmitotics. Their functions are second to none in importance. Normally mitoses are rare; but if there is an urgent demand for extension of the capillary bed they multiply. The swelling preliminary to division must necessarily modify their permeability. Smooth muscle cells go on to death so regularly that reports of their mitotic division are received skeptically in some quarters. If they are capable of division they are to be listed as reverting postmitotics in this provisional classification.

The cell most difficult to place is the fibroblast. It may live and die as a fibroblast playing some little known rôle in fiber formation and perhaps serving other duties as well. It may also divide and produce other fibroblasts, in which event it could be styled a reverting postmitotic. But the lines of distinction between fibroblasts and periosteal cells and between periosteal cells and bone cells are not sharp. If transitions exist, the fibroblast could also be classified as a differentiating intermitotic inasmuch as within this series the individual cell lives are steps toward bone cells.

About the second group of postmitotics there will be less debate. It is appropriate to call them *fixed postmitotics*. They constitute the highest plane of differentiation. After specialized function has been established there is for them no turning back. They age and die. When the body has passed a definite age which is probably not the same for each, nerve cells, rod and cone cells, odontoblasts, cardiac and skeletal muscle cells and many others of individually long lives are not known to multiply. Neither do erythrocytes, granular leukocytes and possibly bone cells undergo mitosis. To extend the list of fixed postmitotics is easy.

In brief, therefore *vegetative intermitotics* are on the lowest plane of differentiation. They exist mainly for the dual purpose of carrying on their own lives and of producing *differentiating intermitotics* whose individual lives in series are steps in the production of postmitotics. The postmitotics are all at the height of specialization in their several spheres. Some, the *reverting postmitotics*, can undergo mitosis; others, the *fixed postmitotics*, are so fixed in their ways that for them this is impossible.

Length of Individual Cell Life

We are concerned with the average length of life of various types of cells under statistically normal conditions. This is emphatically not the same as life span. Adjusting Dublin's definition of the human life span to

cells, the life span of cells can be taken to mean the time limit beyond which the lives of cells of a given type do not extend even under the most favorable circumstances.

To measure accurately the length of life of individual cells is a task of almost insurmountable difficulty. It is not feasible to look into the body with a high powered microscope and to follow a selected cell throughout its existence as an individual The method of continuous observation of cells in tissue cultures is capable of yielding much more information than has been obtained thus far, but many types of cells are difficult or impossible to culture and conditions of life deviate considerably from those within the body Individual cells can be followed in tissue cultures for hours, perhaps for days, but not for months or years. To determine the length of life of cells which wander actively about, or are washed from place to place, is of course more difficult than that of those whose position is fixed, or nearly so, throughout their lives

If only a technique could be devised of marking individual cells in a tissue by inducing them to take up a substance which would be recognizable and would be retained as long as they live, a broad avenue would be opened for advance. In tatooing, a stable dye is introduced into the dermis and for some unknown reason remains localized partly extracellularly and partly intracellularly, the latter in generation upon generation of mesenchymatous cells Further experimentation along this line is indicated. Taking advantage of the fact that bone formation can be dated, by marking the intercellular material formed with a red dye called madder, it should be feasible to get a rough idea of the length of life of bone cells while surrounded by madder

The laborious method of determination of length of life by counting the number of new cells forming and old cells dying, in a cellular population of a single type and number of individuals over a given time, has for obvious reasons not been tried with human tissues. The vague ideas prevalent about length of individual cell life depend chiefly upon impressions (not accurate counts) of the frequency of mitosis

Individual lives ending with mitosis

In general intermitotic cells live shorter lives than postmitotic ones. Inspection of a section of a testicle at the height of sperm production reveals many vegetative intermitotic spermatogonia in mitosis. The mitotic index (ratio of dividing to nondividing cells) is so much greater for such spermatogonia than it is for vegetative intermitotic basal cells of the epidermis as to indicate that their individual lives are considerably shorter. For similar reasons the conclusion is justified that among differentiating intermitotic cells spermatocytes have shorter lives than erythroblasts. It is difficult or impossible to point to cells whose individual lives are shorter than those of spermatocytes, during active formation of sperm. In fact, one mitosis is said to immediately follow the one before.

Among the reverting postmitotics, endothelial cells and epithelial hepatic cells have in all likelihood shorter lives than smooth muscle cells. There is justification for listing ova in this category of reverting post-

mitotics, though, as sex cells they are on a different basis from somatic cells. Most of them die; but, when properly matured and stimulated, they can divide and produce other cells. It is generally conceded that in humans the maximum number of ova is attained at about the time of birth (36,000–300,000, Schröder, 1930) after which the total number decreases. Only a very small fraction matures and ovulates and still fewer become fertilized. The majority live in a kind of trance, waiting perhaps for a chemical messenger from the pituitary to which only a few respond Perhaps ova exhibit a greater range of length of individual life than any other type of cell. In some experimental animals, however, their lives may be shorter. Evans and Swezy (1931) have stated that: "It may even be questioned whether, if we except the elements of the blood, ova do not have the shortest life span of any cells in the body."

For all cells whose individual lives are terminated by mitosis the early initiation of mitosis confers a short life and its postponement a long one. Though mitosis takes place in accordance with the same plan in all cells, little is known about how stimulating and inhibiting factors operate. In response to a deficiency in the number of reverting post-mitotic hepatic cells, some of those present end their individual existences by mitotic division and the production in each case of two in place of one. But other cells, in the number of which there is no deficiency, do not divide in the same way. The stimulus to division is felt only by the particular cell type involved. The nature of the stimulus is unknown and we are equally ignorant as to the mechanism of the inhibition of mitosis which is equally specific in its operation and promotes longevity of intermitotic cells It is not possible even to distinguish with assurance in human cells between intrinsic and environmental factors. But the cessation of mitosis with the formation of the proper number of cells is a fundamental property of organisms. The cellular limit is quite definite in some invertebrates. Van Cleave (1932) has made a statistical analysis of cell number in the gastric glands of *Hydatina* and has found that in the 435 examined every one without exception possessed 6 nuclei. Here the arrest of mitosis is almost certainly hereditary.

Individual lives ending with death

Fixed postmitotic cells are on a different basis. Length of individual cell life is not for them conditioned by stimulation or inhibition of mitosis. It would be mere guess work to try to classify these cells in accordance with the lengths of their lives. But, for those that must be replaced (blood cells, epidermal cells, etc.) life is shorter than it is for others that after an early age is passed are not replaced (nerve cells, retinal cells, cardiac

and skeletal muscle cells, etc.). The central fact stands out that significant differences of great magnitude do exist in the length of life of cells of different sorts.

For lack of data only a rough calculation can be made of the size of these differences. The length of life of the majority of postmitotic nerve cells can be taken to be that of the body less one year. This year must be subtracted because until infants are one year old we cannot be sure that mitosis of nerve cells has stopped. If the average life of the body is 61 years the majority of nerve cells will have individual lives of 60 years or (ignoring leap years) 21,900 days. How long individual neutrophiles live in the bone marrow after their birth at the last mitosis of their myelocytic parent, we have no means of knowing; let us say 4 days. As will be indicated later, some probably die 4 days after entering the circulation. How long the majority live we cannot tell. If 10 days is taken as a conservative estimate then the ratio of their length of life to that of nerve cells is as 10:21,900 or 1:2,190. Of course some nerve cells can and do live much longer than 2,190 days. Neutrophilic leukocytes therefore age and die several thousand times more quickly than nerve cells. Differences in average length of life of individual postmitotic cells of different types in the order of hundreds of times are common.

Factors in length of life

Consider the possibilities of heredity first. In Jenning's view "There can be no doubt that in all animals from the single-celled protozoa through the invertebrates to man, the length of life is largely determined by inheritance. In the fruit flies a single gene may make a great difference in length of life."

The influence of the human fertilized egg on longevity has been graphically described by Streeter (1931). "Whether the infant survives its first year depends in considerable part on the original quality of the egg. If they withstand the usual wear and tear of life until between fifty and sixty years they conform to the actuary's expectation of life, at birth—*and to the embryologist's expectation of the performance of an egg of* average quality. It is only the extraordinarily good egg that is still going strong at 80 years, and we see him (or her) do this in the absence of any exquisite hygienic régime or experimental favor." He goes on to explain that " The egg as a whole, of course, consists of a multitude of elements and it is the sum and integration of these that determines its fate." Some of its parts may lead to hardy, long lived tissues and others to tissues handicapped at the start. Thus, mortality tables become intelligible "if one accepts the point of view that there is an egg-determined life span and an egg-determined vitality of individual organs." It is possible that

the length of the individual lives of cells of many sorts, like their vigor, is determined in some measure by heredity.

Manner of cell life may also be involved in longevity. Pearl's (1928) generalization that "the faster an organism lives the sooner it dies" may apply to cells. It has long been known that the length of life of a wide variety of lower forms is increased by reduction of food. Observations on increase in length of life of rats, caused by supplying a diet adequate for maintenance but insufficient for growth, are of particular interest (McCay, Chapter 6). One result of curtailment of food may be reduction in rate of chemical change. The earlier studies of Jacques Loeb and Northrop (1917) are also of interest. They found that the length of life of the fruit fly is, within certain limits, a function of temperature. With increase in temperature its life is shortened. Increase in temperature speeds up most chemical reactions.

This line of argument seems to hold together, but evidence is lacking as to the existence of differences in rate of living, food intake and temperature of cells whose lives show such great differences in length. All kinds of quantitative measurement increase in value in physiology with the nearness of their applicability to individual cells. It is so with determinations of basal metabolic rates, easily made for whole organisms, feasible for some tissues but not possible as yet for individual cells in their natural environments. However it is a fact that the temperature of different parts of the body is far from uniform. Mann (1932) quotes Michel as stating that the temperature of the cornea is 10°C. lower than the rest of the body. Huggins, Blocksom and Noonan (1936) report that the central bone marrow is 4–8°C. higher than that of bones of the extremities (tail). Other examples could be cited. Slight differences of other sorts in environment may be not without influence on length of cell life.

To summarize it appears that, barring accidents, length of intermitotic cell life depends upon factors that promote or inhibit cell division. For postmitotic cells length of life seems to be conditioned by the ability to maintain their characteristic structural organization in the continual adaptation that they must make to changes in their tissue fluid environments. It is a fallacy that degree of differentiation of itself determines length of cell life.

Cellular Death

The individual lives of intermitotic cells end with the production from each of two other individuals by mitosis; but the stream of protoplasm remains alive and is continuous from one generation to another. The individual lives of humans are terminated by the death of all the cells

that they posses at the time; but in case they have offspring a narrow stream of protoplasm remains alive and is continuous through the sex cells from generation to generation.

Our task here is not with the protoplasm that continues to live, despite the loss of individuality, but with the death of postmitotic cells at the ends of many trails in the body, that is to say with the living streams that finally dry up. It would be nice to be able to distinguish natural death of cells following uncomplicated ageing from death due to other factors such as injury and disease, a differentiation perhaps a little easier made than that between natural and pathological death of bodies but, nevertheless, extremely difficult.

A human being is pronounced dead when the circulation fails, consciousness is lost and there is no longer a possibility of resuscitation. But he is then not wholly dead, because some of his cells continue to live for varying periods. The heart can be made to start beating again when removed from certain executed criminals. The nerves remain alive; for, by their stimulation, muscular contraction is produced. Lewis and McCoy (1922) have found that in "killed" animals left at room temperature some types of cells may survive for 120 hours.

Similarly it would be premature to assert that an ageing cell has died while a spark of life remains. Functions characteristic of youth and maturity can and do drop away. Even the nucleus can be lost though oxygen consumption persists to some extent. Thus Harrop (1919) observed that masses of nonnucleated red blood cells have an oxygen consumption proportional to the number of reticulated cells among them. When such cells were absent he was unable to detect any oxygen consumption. Death is always piecemeal for humans and it is so for a few types of individual cells. Necrobiosis is for Minot (1908) a condition in which the cells continue to live but change their chemical organization so that their substance passes from a living to a dead state. "Here life and death play together and go hand in hand."

We agree with Lepeschkin (1931) that an organism or a cell can only be called dead when all of its living matter is dead. Obviously the absence of all vital manifestations is not sufficient. Frozen cells can apparently endure in a state of suspended animation (vitrification) indefinitely; but they are not dead, since they still retain the structural organization, which, when unlocked by increase in temperature, confers renewed vitality (see papers by Luyet, 1938 and others). Death is disorganization of living matter which makes permanently impossible any and all vital phenomena.

What normally are the lethal factors? It is natural to look again to heredity and environment. There is, for example, a lethal factor connected with yellow fur in mice. When received from both male and female

sides it is always fatal to the embryo (Little, 1917; Kirkham, 1919). Whether this factor operates on the cellular level restricting the lives of individual cells or on the higher organismal level preventing the necessary coöperation between many cells is a mystery.

The environment of some cells is definitely more favorable than that of others. Long lived nerve cells are carefully shielded from mechanical injury. Probably, however, of at least equal importance is the close regulation of their tissue fluid environment. As related in Chapter 2 changes in the cerebrospinal fluid with age are almost negligible. Neutrophile leukocytes, on the other hand, have a far greater occupational hazard. The environments in which they may be called to serve include all those that exist in the body some of which doubtless change materially with age. Epidermal cells are edged away from the blood stream by the production of new generations of cells nearer to it. Death for them is an inevitable result of this displacement. How long they would live if they were not displaced is problematical. Many cells die; because, as they grow older, their adaptability decreases and they become more vulnerable to adverse environmental conditions.

In a crude way we can recognize individual cell death microscopically This may be difficult in ordinary fixed and stained preparations but the frequent shrinkage and characteristic appearance of nuclei in postmortem degeneration of the body is familiar to pathologists. Evans and Schulemann (1914) remarked upon the extraordinary rapidity with which dead cells take in vital benzidine dyes and the diffuse, uniform coloration that ensues. In cells supravitally stained with neutral red Lewis and McCoy (1922) employed the following criteria for death "(1) loss of color from the granules and vacuoles, (2) diffuse pink staining of the cytoplasm and nucleus, (3) the appearance of a sharp and distinct nuclear membrane and a change in texture of the cytoplasm and nucleus" Using dark-field illumination W H Lewis (1923) observed the appearance in dying cells of certain very small brightly shining (white) bodies which he called *d* or "death granules" These were first in Brownian movement which soon ceased. To quote Lewis "During the period when the cells were dying, spherical blebs often appeared on both the flat and rounded cells These were pale grayish sacs with very thin walls and fluid contents in which varying numbers of small white granules in active Brownian motion were seen The blebs varied in size and were occasionally as large as a contracted cell. Sometimes the blebs were so crowded with granules that they were milky in appearance Frequently one would burst, freeing its granular contents into the surrounding fluid medium where they showed Brownian motion until they settled down on the slide." Luyet's (1937) *method for the differential staining of living and dead plant cells* may prove of value for animal cells also

Death surely comes to cells in many ways. Its *modus operandi* may well be different in cells of the same type, and much more so in cells of different sorts whose structural organization will in part determine which alterations are possible. In general, there is an increase in permeability

of cellular and nuclear membranes and a coagulation of cytoplasm and nucleoplasm before solution or fragmentation of the cell.

Cellular Immortality

Much less is heard now-a-days than a generation ago about cellular immortality. When tissues were first cultivated outside the body and life could be maintained by repeated transfer to fresh media long beyond the life span of the body whence they came and apparently indefinitely, this was said to be evidence of the potential immortality of the cells in question. The continued vitality of special groups of tumor cells transferred from one susceptible animal to another, likewise far beyond the life span of the animal to which they were native, was similarily taken as proof of their potential immortality. Gradually the idea was conceived that all cells are potentially immortal.

That there was in these experiments continuity of living protoplasm is *clear. But most of us think that the protoplasm of all organisms living* at present has been continued to them in an unbroken line down through the ages. However, we are dealing with cells as individuals. In all of these vital streams individuals certainly come and go, age and die.

Yet a close examination of various publications gives the impression that the writers believed in the existence of potential individual immortality of cells. One of Pearl's (1922) main conclusions is "That the individual cells and tissues of the body, in and by themselves, are potentially immortal." He quoted Jacques Loeb as saying that "death is not inherent in the individual cell." On the basis of much experience, Child (1930) has expressed the view that: "If we could control character and amount of nutrition of a cell with sufficient accuracy, it might even be possible to keep it physiologically young indefinitely without division."

Examples of Ageing of Individual Cells

Whatever the length of life of individual cells they change progressively with time. The alterations are spoken of as *age changes* whether they occur at the beginning, during the middle or toward the end of cell life. Some are evidenced by detectable differences in behavior and others by observable differences in structure but most of them elude us. To determine the ageing of cells of a single type is a task which will probably never be accomplished, for full knowledge is prerequisite of normal or usual structure and function at every interval of life in order to bring out the changes in them with time.

The *processes of ageing* are to be distinguished from age changes. They are the underlying alterations of which the age changes are the manifestations. To discover their nature is far more difficult. Their number may

be less, for it would not be surprising if one and the same process of ageing were to reveal itself by different age changes in cells of different types. Assuming that decrease in metabolic rate is one of them, the specific functional attribute lost (the age change noted) is hardly likely to be the same in phagocytic, contractile, secretory and conductile cells. In this chapter and in this book a great many age changes are described. The processes of ageing are in the background almost wholly hidden from us.

The ageing of cells whose individual lives are cut short by mitosis is obviously different from that of those who grow old and die. It is not to be expected, however, that even in the lives of vegetative intermitotics (epidermal basal cells, etc.) age changes are lacking. There is probably an interval between the beginning of individual life after mitosis and its end with the next following mitosis during which the cell changes within its hereditary potentiality and under the influence of its environment.

In the words of Child (1930), "senescence appears to consist essentially in a gradual decrease in the amount of chemical change independent of external stimulation, and in the amount of new protoplasm formed by a given amount of protoplasm, in a given time." During the lives of vegetative intermitotics new protoplasm is formed and it is unlikely that the speed of its formation is uniform throughout.

Conklin (1924) has reminded us that the nucleus is largest in the prophase before its membrane disappears and smallest in the anaphase when it consists only of daughter chromosomes. He has stated that "in general, the longer the interval between mitoses, the larger the nucleus becomes," further that the great size "of the nuclei of nerve cells is dependent in part upon the length of time since the previous mitosis, during which the nucleus continues to grow." We note that he has wisely qualified his statements by saying "in general" and "in part." In vegetative intermitotics the nucleus is small at the close of the telophase when the two daughter cells are starting on their individual existences and much larger in the prophase, near the end of their individual lives.

The curve of growth of these cells, throughout their lives, has not been established. It may rise sharply to begin with and reach a kind of plateau. Whether there is even a slight decrease in size of the whole cells (despite increase in size of their nuclei) before their individual lives are terminated by division, we do not know. However, constructive metabolism would appear to give place to maintenance metabolism. The dictum of Minot (1908) that "The period of youth is the period of most rapid decline" would apply to these individual cells if it could be proved that the rate of metabolism per unit of volume decreases. If so, this would also be a fundamental age change. In the event of injury mitosis might be delayed, length of individual life might be extended beyond the regular life span,

and age changes not usually seen might occur. Severe injury leading to death would make these cells postmitotics; for they would not divide again and degenerative alterations, not normally encountered, might take place.

Investigation of the ageing of differentiating intermitotics presents similar problems except that at some time during their lives there is progressive specialization. In the erythroblasts, for instance, which after an unknown number of generations produce fixed postmitotic red cells, there is a decrease in cytoplasmic basophilic material and an increase in hemoglobin. Inheritance of such acquired characteristics is a property of both differentiating intermitotics and reverting postmitotics. In the differentiating intermitotics, as in the vegetative intermitotics, evidences of senility going on to death are normally absent.

Though reverting postmitotics, serving the body in the fashion intended, can undergo mitosis and thereby terminate their lives without senility, most of them die eventually like the fixed postmitotics with which we shall consider them. It is the presence of this downswing of the curve of life which adds to their lives an important phase absent, or at least inconspicuous, in the normal lives of vegetative and differentiating intermitotics. There is more to study, in another sense, because their individual lives are generally longer. Some of them are so long that our information is patchy and relates only to parts of their lives, for one investigator not infrequently takes the senile end and the other the beginning and the two sets of observations do not meet in the middle.

It is obviously necessary to start with the structure and function of cells of a given type immediately after the cessation of mitosis and to trace the changes they undergo to normal death; because to follow an individual cell all this time is impossible. "Normal death" is specified because injury might bring about death prematurely and so quickly that alterations usually occurring before death would be absent. Naturally the age changes will, in part at least, depend upon the particular function which is acquired, served and lost and the structural organization inseparably linked with it. It is tempting to try to generalize, but what is needed most at present are quantitative data based on intensive study of individual cell types. Only a few are selected for brief presentation here.

Nerve cells

Nerve cells perhaps lend themselves best to studies on ageing though they must be examined collectively since the life of individuals cannot be followed. Their lives in the central nervous system after their cellular community passes the one year mark are all postmitotic. The beginning of individual lives can in some cases be still more accurately dated for the particular type of cell chosen. The type should be one the functional

capacity of which is most susceptible of measurement. The numbers that die off relative to the whole at different ages of the community will have to be determined in order that the necessary correction can be made in functional load estimations for the individual survivors. The whole cell must be included. Owing to dictates of technique one group of workers concentrates on the processes and another on the cell bodies. It is necessary to join their results together. Since functional changes are to be correlated with structural ones, the conditions of experiment should be as ideal as possible. In other words, the control animals should resemble those subjected to experimental procedures as closely as possible. Thus, for his study of the effects of inanition at different ages, Andrew (1939) has wisely employed mice of a closely inbred strain (C57) of which the individuals are more alike than any two humans except identical twins. But unfortunately mice are too small for some kinds of physiological experimentation.

In the selection of properties of nerve cells for investigation that change with time, one is almost embarrassed by the number that present themselves; whereas with vegetative intermitotics the number was found to be so small that it was difficult to find a foothold. A few may be mentioned almost at random for this account has no pretensions to completeness.

Nucleus and cytoplasm, containing mitochondria and Golgi bodies, are inherited from antecedent intermitotic nerve cells. Early in cell life of the fixed postmitotics there is a change in shape with extension of one or more processes. About this time neurofibrils and Nissl substance appear. Myelinization becomes fairly complete in the chief fiber tracts in children 3 years old (Turpin, 1934) but the processes of some cells never become myelinated. Intracellular oxidases are said to decrease as myelin is laid down (Marinesco, 1922, 1924).

Behnsen (1927) has observed that nerve cells are easily stained vitally with trypan blue in young animals—a property which is lost by them in adults. But whether this is due to an age change in the nerve cells or to a decrease in the vascular permeability of older animals which prevents the trypan blue from reaching them, further work alone will show.

Young mice have been found to be less resistant than older ones to several animal passed strains of neurotropic viruses (Olitsky, Sabin and Cox, 1936; Casals, 1940 and others). King (1940) has confirmed the observation of Olitsky, Sabin and Cox but has failed to find differences in susceptibility of mice with age to freshly isolated samples of equin encephalomyelitis virus. Before any conclusion is reached on the presence or absence of a difference in susceptibility of nerve cells of different ages to viruses, it is necessary to check on particle size and particle linkage with nonvirus material of passed (or fixed) viruses and of fresh (or street)

viruses, effective contact of virus with cells and on several other points including the increase in production of neutralizing antibodies with age (Morgan, 1940). This increase can begin even during intrauterine development (Dettwiler, Hudson and Woolfert, 1940).

In normal ageing of nerve cell bodies Andrew (1939) has found "a shrinkage of cell outlines; a loss of Nissl material; a change in the nucleus in the direction of amitotic division (for instance, division of the nucleolus and lobulation of the nucleus or actual nuclear division); and a granulation of the Golgi apparatus." It is interesting that similar changes may occur in inanition, though severe starvation can bring about different results. Kuntz (1938) has determined the increase in incidence of "melanotic pigment" in human sympathetic ganglion cells with increasing age of the body. The fact that some remain free of pigment is important for it illustrates the point that individual cells of the same type age in this respect at different rates. He also observed significant modifications in the processes of these cells with age.

Truex (1940) has provided data on increase in fatty degeneration of Gasserian ganglion cells. This, as well as a decrease in the number of myelinated dorsal root fibers (Corbin and Gardner, 1937; Gardner, 1940), may be correlated with the clinically established decrease in somatic sensitivity after the third decade reported by Pearson (1928). Truex has called attention to the increase in fatty degeneration with age of tissue cultures of spinal ganglia of chicks (Weiss and Wang, 1937). He has also expressed the view that the fatty degeneration in its early stages may be reversible, that the cells may return to "normality"—a belief suggested by Ranson's (1909) description of regenerative changes in the large cells of spinal ganglia after neurotomy. Decrease in oxidative processes would lead to increase in fat and increase in oxidative processes to its removal. Neuronophagia (a process of lysis and digestion of nerve cells) is a terminal phase in the lives of certain types of nerve cells in senile persons (Andrew and Cardwell, 1940).

Cottrell (1940) has investigated age changes in human peripheral nerves from the first to the 8th decade. The most outstanding alteration "is that of increase in connective tissue elements, which is concomitant with reduction in potency of the blood vessels and destruction of the nerve fibers." This is suggestive of a modification in the tissue fluid environment. Measurements of function of peripheral nerves are especially valuable when they are supported by histological observations (Heinbecker, Bishop and O'Leary, 1936). This double approach, which has been employed to great advantage by these investigators in the study of poliomyelitis (O'Leary, Heinbecker and Bishop, 1932), should be used in a

comprehensive examination of age changes in nerve fibers. Moreover, as in poliomyelitis (Covell, 1932), the alterations in the peripheral processes should be correlated with changes in the cell bodies within the spinal cord.

The vista of possible correlations expands with every new advance. Polarization optical methods have shown (Schmitt and Bear, 1939) that the axon sheath is qualitatively similar for all types, vertebrates as well as invertebrates; since the lipide molecules are oriented with their long axes parallel and the protein ones with their long axes tangential to the axon the two constitute a concentric, many-layered envelop. Taylor's (1941) investigations on the earthworm are particularly significant. It will probably not be long before this "ultrastructure" is studied in young and senile nerves.

Though there may be and probably is a fundamental similarity in the ageing of all nerve cells, the possibility of differences in different types and in individuals of the same type in different species has to be borne in mind. *It is impossible at present to unscramble the results and piece together* a consistent integrated account of even the most noticeable changes for any one type. Within a given type in a single species the ageing of individual cells is not uniform. There appears to be an element of competition in all cell life; the weak tend to go under before the strong. But this competition is usually held well within bounds.

Skeletal muscle cells

Skeletal muscle cells have been somewhat less studied but the literature [illegible]

attention. Later age changes in size have been accurately determined for humans by Bucciante and Luria (1934). Their size increases greatly and their number decreases. A parallel increase takes place in the volume of the intermuscular tissue so that we may hypothecate an alteration in their tissue fluid environments as in the case of nerve fibers. In other instances however (brown atrophy) the muscle cells are said to become thinner with age and to accumulate lipofuscin—the "wear and tear" pigment of Aschoff. Physiological investigation of responsiveness and contractile power have not accompanied the morphological studies. Obviously both should be correlated with micro-chemical determinations from beginning to end of the lives of the cells and pains taken, as always, to eliminate alterations brought about by disease and injury. Numerous pertinent histochemical facts about the ageing of muscle are given by Lowry and Hastings (Chapter 5).

Epidermal cells

Epidermal cells can on the contrary be easily investigated in humans for it is a simple matter to make biopsies. To study their postmitotic lives it is again necessary to start with cells that do not undergo mitosis. This presents considerable difficulty in individual cells of the spinous layer. But those situated nearest to the surface are probably fixed postmitotics. With age there is a change in shape, a decrease in mitochondria, an increase in keratohyalin granules, a decrease in size, progressive keratinization and dehydration. These are but the most outspoken alterations. Available microchemical and microphysical methods will doubtless reveal many more. Viscosity changes can, up to a certain point, be measured by degree of displacement under ultracentrifugal force (Cowdry and Paletta, 1941; Paletta, Cowdry and Lischer, 1942).

Physiological modifications of epidermal cells with age will be more difficult to follow than in the case of nerve and muscle cells whose specialized activities are easily measured. But epidermal cells have the advantage that by a judicious selection of specimens the influence of many naturally occurring conditions on ageing can be contrasted.

(1) It may be helpful to compare extended, or protracted, ageing of cells with ageing reduced to a minimum of stages. In the palms of the hands and the soles of the feet where the epidermis is thick there are many more layers of cells than in protected situations where it is thin In the latter the stratum lucidum is absent and the stratum granulosum absent or but poorly developed so that the postmitotic spinous cells age and die as corneal cells without showing the granular and lucid phases so conspicuously as in thick epidermis.

(2) The influence of the external environment is important. Comparison of age changes in exposed epidermis with those seen in congenital and implantation dermoid cysts is indicated. In the cysts the epidermal cells are not exposed to the same wear and tear or to ultraviolet light Desquamation is probably much less than from the epidermal surface of the body and mechanical forces are quite different. Epidermal structure, once formed, is simply maintained over a great many years especially in the congenital dermoids One would not expect the same rate of change in cellular population as in exposed epidermis. A detailed comparison might reveal still other contrasting conditions not without influence in moulding the lives of the cells. Early literature on the experimental production of implantation dermoids is reviewed by Ewing (1940).

(3) A marked feature in the ageing of epidermal cells is the formation of keratin It would therefore be desirable to contrast the sequence of events in epidermal cells

Neutrophilic leucocytes

Neutrophilic leucocytes will serve as a final example of fixed postmitotic cells chosen because, in their individual lives, there is a greater factor of chance than for any other cells due partly to their high motility and to the wider variety of environments to which they must adjust themselves. A well balanced account of them and their functions has been supplied by Bunting (1938).

(1) *In the bone marrow.* Individual neutrophiles begin life as the daughter cells produced by the last division of a myelocyte. Unfortunately, we cannot definitely identify the last division of a myelocyte nor can we follow the career of any single neutrophile except in the unnatural condition of tissue culture. It is clear however that a neutrophile does not attain the size of a myelocyte. It is also evident that before leaving the bone marrow and entering the circulation its nucleus becomes more polymorphic than that of its parent cell. At the same time it is fair to assume that motility and phagocytic powers increase

(2) *In the blood stream.* As neutrophiles are carried along, they are capable of phagocytosing certain particulate materials with which they may chance to come in contact. If this happens, their lives are probably modified thereby. But normally the great majority of neutrophiles do not experience such contacts.

Exactly how long, on the average, they remain in the circulation has not been discovered. Roberts and Kracke (1930) have observed a complete disappearance of neutrophiles from the circulation within 4 days after the decrease began in a patient suffering a recurrence of the condition of agranulocytosis. If, during these 4 days, no young neutrophiles entered the blood from the bone marrow and those that were present disappeared at the same rate as in a normal person, the average time of sojourn of these cells in the blood stream could be placed at somewhat less than 4 days. Weiskotten (1930) has reported the disappearance of rabbit leucocytes, which correspond to human neutrophiles, from the circulation 3–4 days after the production of new cells was prevented by injury of the marrow with benzol. The similarity in the time of disappearance lends support to both observations.

Neutrophiles in the circulation have been listed in five classes of increasing age by Arneth (1904) depending upon whether they possess 1, 2, 3, 4 or 5 (or more) nuclear lobes. In Schilling (1929) counts three types of neutrophiles (juveniles, stab nuclears and segment nuclears) are recognized, characterized by increasing nuclear polymorphism and by certain other features, in the transition from youth to maturity. Valuable data on the maturity of neutrophiles in the circulation are unquestionably to

be obtained from such counts. But Bunting (1932) reminds us "that leucocytes with basophilic protoplasm, loosely woven nuclei and even with basophilic granules among the neutrophilic granules, and thus obviously young cells, may show as many lobes to the nucleus as cells evidently senile." He also calls attention to the excessive lobation (8 or 9) in certain pathological states. When neutrophiles are examined at intervals in blood isolated in veins between two ligatures, development from one class of Arneth to another is not observed; but when blood is thus isolated in which the number of young forms is first increased by stimulation of the bone marrow development from class 1 to class 2 can be demonstrated (Climeriko and Ponder, 1934). According to Crosman and Charipper (1938) increased functional activity brings about an increased lobation in a shorter time than that required to produce a similar lobation with time alone as a factor.

Numerous other age changes have been described. Schilling (1908) was the first to notice non-motile neutrophiles in blood examined in the dark field. Sabin later observed similar cells in which she (Sabin *et al.*, 1924) failed to find mitochondria with Janus green. Decrease in motility and in mitochondrial content are both to be expected as neutrophiles age. Other senile, or dead, cells lose mitochondria and specific functional attributes. How general are these alterations in the period under consideration has not been accurately measured.

Smith and McDowell (1929) have been unable to confirm the idea that large numbers of neutrophiles die in the blood stream and think that the dead, non-motile cells are often technical artefacts. According to Maximow and Bloom (1937), "The presence of degenerating leucocytes in the circulating blood, although often described, has never been confirmed experimentally." If 3–4 days is accepted as the duration of their residence in the blood stream, one-third to one-fourth of the total number present must be removed from the blood in some way each day. Many are filtered out by the spleen and the liver to be destroyed by reticuloendothelial cells; but in the absence of counts of non-motile leucocytes in blood entering and leaving these filters, two possibilities remain: either that these cells are removed with extraordinary speed from the circulation or that only a very small, almost negligible, proportion of neutrophiles age and die in this way because they are so seldom seen in the blood. The neutrophiles, which remove themselves from the circulation by entering tissue fluids, do not figure in this estimate because it is concerned only with the frequency of neutrophiles which lose their lives and cannot emigrate.

(3) *In tissue fluids.* Leucocytes may happen to be washed through vessels the endothelial linings of which have, for some reason, become sticky so that they adhere to the vessel walls. Correlated with this, but some-

times independent of it, the blood stream may be slowed or temporarily stopped. It would be a mistake to assume that either of these conditions is necessarily abnormal though both can result from injury. However they favor the passage of neutrophiles through the vessel walls and their entrance into the surrounding tissue fluids. In pathological states this migration of neutrophiles can occur in any part of the body so that the environments entered can be of wide variety especially since some of the environments probably change with ageing of the body. That they normally enter certain tissue fluids is assured as will appear later.

The only detailed account of their age changes in tissue fluid we owe to the Clarks (1936). These investigators studied the finely granular leukocytes of rabbits, which correspond to human neutrophiles, in special chambers inserted into the ears. After passing through the vessel walls the leukocytes move about in the tissue fluid for a day or two, phagocytosing any materials that appeal to them, come to rest, round up, lose their nuclear polymorphism and, before they die, assume an appearance reminiscent of non-granular leukocytes (lymphocytes).

(4) *In lumina connecting with the outside world.* Though many neutrophiles age and die in the tissue fluids, some travel further afield. Isaacs and Danielian (1927) have reported that neutrophiles escape into the mouth in saliva and have considered it likely that they also escape through the mucous membrane into other parts of the alimentary tract. Perhaps, in this extracorporeal location, some of the neutrophiles are still able to phagocytose bacteria. The authors concluded that this method of elimination is a regulatory mechanism for maintenance of the proper number in the blood. Bunting (1938) found neutrophiles in the salivary ducts but did not commit himself on the conclusion reached by Isaacs and Danielian. The literature contains many accounts of similar escape by lymphocytes and eosinophiles.

Stockard's (1932) description of the escape of swarms of leukocytes of the same type (but not neutrophilic in the mammals studied) into the vaginal fluid during the third stage of estrus is particularly significant, because, in this case, they definitely serve useful functions which he has specified. Neither the genital nor the alimentary escape would be possible unless the leukocytes had first left the blood vessels and had entered the respective subepithelial tissue fluids. Neutrophiles are certainly great travellers.

The foregoing examples indicate that the ageing of each cell type is a problem in itself. They also show that concentration of available resources and time on a single cell type is necessary in order to make progress. In choosing the cell type it is important to find the one that is most accessible to techniques—chemical and physical, physiological and morphological—

likely to yield quantitative data. Only when changing properties can be plotted against time in a constructive way can we hope to approach the unknown and basic processes of ageing which are conditioned by heredity and moulded by environment.

General Changes in Ageing of Cells

The time has not arrived for generalizations. Yet some that have been advanced are interesting and possibly destined to receive more support.

Nucleocytoplasmic ratio

Volumes have been written by Minot, Hertwig and their followers on changes in the nucleocytoplasmic ratio. That this ratio does decrease with age as claimed by Minot in some cases—in fact in many cases—is beyond question; but Wilson (1925) has considered the matter critically and has pointed out significant exceptions.

Interesting is Conklin's idea that the volume of the nucleus increases with the length of individual cell life. Some large nerve cells possess larger nuclei than any other cells in the body except ova and both are very long lived. But there are small nerve cells of equal age that have small nuclei. In the later lives of certain cells, the converse happens and their nuclei definitely and regularly decrease in volume (postmitotic epidermal cells). A complicating factor in the interpretation of changes in nucleocytoplasmic ratios in the lives of individual cells is the fact that both nucleus and cytoplasm undergo alterations during the period which are not brought out by simple determinations of volume. Thus a large nucleus may contain less thymonucleic acid than a smaller one, intranuclear viscosities may be very different in nuclei of the same size (Cowdry and Paletta, 1941) and cytoplasms of the same volume may differ greatly in their content of water, fat, pigment, secretion antecedents and other materials.

Brailsford, Robertson and others have attempted to determine chemical nucleocytoplasmic ratios. Using his method, Dawbarn (1932) has investigated a ratio calculated by dividing the nucleic acid nitrogen by the total coagulable nitrogen less nucleic acid nitrogen during development of white mice. She obtained a ratio which was high at 35 days of age, which decreased rapidly, then slowly and finally slowly increased to 700 days, at which age it was much less than to begin with. But entire animals were of necessity analyzed so that this information was obtained at the sacrifice of being forced away not only from a consideration of individual cell life but also that of particular tissues.

Decrease in active protoplasm

The word *protoplasm* properly denotes both nucleus and cytoplasm. The effective relative amount of active protoplasm would be decreased

if the proportion of the inactive variety were increased. To distinguish between the two is by no means a simple matter. There is a general feeling that those investigators who would have us believe that the cell consists of living and lifeless (paraplastic or metaplastic) materials have overstepped the mark. But that some cells contain storage (deutoplasmic) materials, which, during the phase of storage, are not actively involved in chemical change is correct. However, such substances are usually found in young or potentially vigorous cells, not in senile ones. In the fatty degeneration and pigmentation of nerve cells and in the accumulation of keratin in epidermal cells, the proportion of active cytoplasm is reduced but these are consequences of ageing or altered environment rather than factors productive of ageing. To intimate that ageing inevitably results from a progressive clogging of the cell with materials incapable of participating in chemical and physical adjustments to their environment is unjustified.

Decrease in water content

Lowry and Hastings in Chapter 5 present evidence that a change in the water content of many tissues seems to occur in senescence; but that, in spite of the widespread belief to the contrary, the change is a hydration rather than a desiccation. This increase in water may, they say, be quite possibly an extracellular edema, and may be consequent to atrophy, the loss of tissue cells, or even to cardiac or renal hypofunction. Actual evidence for change in the composition of the cytoplasm that remains functionally active in the very old individual is, in their opinion, still lacking. They are tempted to postulate that *a given cell type regardless of age has a composition restricted within narrow limits.*

The histochemical methods employed by these investigators provide valuable facts about the whole body and concerning certain tissues made up of myriads of cells and other components. We do not question the increase in water in the tissues examined. The condition of the water may not remain constant. According to Thoenes (1925) water is more firmly bound and in larger proportion to colloids in young tissues than in older ones. Information is awaited about numerous substances other than water entering into the composition of cells. The very old individual contains, of course, a considerable total volume of cytoplasms belonging chiefly to many long-lived fixed postmitotic cells (nerve, skeletal muscle, and others). But there are in addition numerous short lived young cells in the tissues that undergo replacement as long as the body lives. Nevertheless the postulate about a given *cell type* may hold in some instances. It is possible also that during a considerable fraction of the lives of individual cells their composition is restricted within narrow limits. Still it remains

to be proved that this restriction holds regardless of age, in other words, unto death. Examples can be brought forward of individual cells whose composition is not restricted within narrow limits throughout their lives. The amounts of keratin, pigment, hemoglobin and a wide variety of other substances increase with age during individual cell life. Others, such as chromatin, decrease in certain cells and the water content itself may decrease also.

Ageing of colloids

Herbert Spencer (1866) emphasized the colloidal nature of protoplasm and suggested that ageing results from a progressive increase in protoplasmic stability, "an approach toward molecular equilibrium." With justice, Wilson (1925) has written "It may be doubted whether any later author has offered a more satisfactory interpretation of senescence, though many have endeavored to render it more specific."

Růžička (1924) and his associates have investigated the progressive condensation of colloids in living protoplasm—a process which he called "hysteresis." It is brought about by a gradual decrease in the electric charges on the colloidal particles which reduces their dispersion (i.e. promotes condensation). This, in turn, reduces chemical activity.

Wells (1933) makes the point "that repeated alteration in degrees of dispersion of colloidal gels or emulsions decreases their capacity to reversal towards the original degree of dispersion," which is important in connection with M. R. Lewis' (1923) experimental production of reversible gelation in living cells of tissue cultures.

In commenting on certain views expressed by Rocasolano (1924) Wells has summarized his thesis in the following words: "Ageing is a process of dehydration and coagulation tending toward a chemical equilibrium, brought about by changes in the adsorption complex and by reduction in electrical charge. Dehydration is followed by a decrease in the total surface of the micell, and hence of energy and electrostatic capacity, and by a decrease in viscosity, resulting in decreased metabolism and regenerative capacity."

Valuable information about the ageing of colloids and many other substances *in vitro* is given by Dhar (1932) and is supplemented by literature references. The assumption that similar phenomena take place in living cells is useful but the intracellular environment cannot be duplicated in any test tube. Chemical and physical "laws" probably hold though they may be conditioned in their operation by a host of factors some suspected but many still unknown. There is also the great difference that whereas substances age regularly with time in laboratory experiments, there is

in the living cell a continual breaking down and elimination of old material and a building up of new in all likelihood at special rates for each substance. Vital ageing depends, therefore, upon the operation of these physical laws on materials renewed in an even more sluggish way as the time passes by for the particular cell.

It is possible, in the long view, that all types of cells undergo in common basic alterations, which may be obscured by special properties, which alterations take place at a tempo peculiar to the cell type and which partly condition its length of life. Yet Child is of the opinion that: "In the light of present knowledge it appears improbable that we shall ever be able to distinguish any single reaction or particular physicochemical change in protoplasms as the fundamental factor in the process of growing old or growing young."

Is Ageing of Cells Reversible?

There is no doubt that groups of cells can undergo dedifferentiation, can lose structural differentiations and the special functions connected with them. They then look less mature. The frequency of mitosis may increase and be counted as a second sign of youth. The term anaplasia (Gr. *ana*, again + *plastis*, moulding) is sometimes employed to designate such a remoulding of tissue.

But we are trying to focus this account on individual cells. Whether dedifferentiation occurs within the individual life of a cell is extraordinarily difficult to discover. Individual dedifferentiation may not be an essential factor in the dedifferentiation of a tissue composed of hundreds of cells.

When the dedifferentiation takes place slowly, there may be an opportunity for the cellular population involved to change its personnel. If this happens, it is possible that dedifferentiation of the whole tissue is occasioned, either by some modification (other than dedifferentiation) in the cells originally present which causes them to form other cells incapable of differentiation like their parents, or that the new cells produced from them possess this potency but fail to realize it owing to some alteration in their tissue fluid environment. That these environments should remain constant is unlikely because dedifferentiation of tissue usually accompanies a radical injury of some sort.

When, on the other hand, dedifferentiation is quickly effected, the chances are greater that individual cells undergo dedifferentiation because there is less time of mitosis. Arey (1936) has stated that in tiny wounds of the epidermis of fishes and amphibia epithelial continuity can be regained in as short a period as 3 hours. He and Covode have observed that

corneal lesions in mammals can heal in 6 hours. But in these cases dedifferentiation of tissue may have been absent or slight.

According to Ferguson (1928), who worked under the expert guidance of Arey and Bensley, "After the cells of the adult gastric gland are differentiated they apparently retain the inherent possibilities of the original cells from which they spring . . . all the cells, with the possible exception of the parietals, are capable of reverting to a more primitive cell type under altered conditions." But it is not clear that the reversion takes place in their individual lives.

The best case for dedifferentiation has been described by Boling (1935) in the marginal cells of ciliated epithelium 6 hours after injury. However, the loss of cilia, or the loss of any specialized function, though it can properly be called dedifferentiation, is not by itself a reliable criterion of reversal in the processes of ageing—of return to a more youthful state. Decrease in specialized function as the cells become feeble is indeed one manifestation of ageing. Something more than loss of differentiation must be proved before we can accept the particular case as one showing reversibility of ageing in the life of an individual cell. The cell, after reversion, must exhibit organization and related function typical of an earlier stage in its life. The arrest of ageing in reverting postmitotics is not a reversal of ageing. Their individual lives cease when they divide to produce two other individuals which function at about the point where they gave up.

The dedifferentiation of certain individual protozoa can be accepted as a fact. When their vitality is diminished they may encyst, undergo extensive reorganization and emerge with enhanced vitality. In their lives ageing can therefore be both arrested and reversed. But, as Jennings has pointed out, protozoa are very different from the tissue cells of higher forms. The latter do not possess reserve parts which can be substituted for those which may become exhausted. Moreover, adjustment to environment is made easier for them than for protozoa for the properties of their tissue fluid surroundings are regulated.

But there are no *a priori* reasons why a reversal should not take place in human cells. Many chemical and physical changes are involved in cellular ageing. Some of these are reversible in the test tube and they may also be reversible in the cell. Not only certain protozoa but also some cells of invertebrates can dedifferentiate. This property may not have been irretrievably lost in the evolution up to man. It is an obvious truism that the cells making up the human body are of many sorts. To claim that such a property is lacking in all of them would be unwise. Let us be content for the present with the general concept that with increase in fixity of their internal organization the possibility of reversal decreases.

Changes in Cell Life with Ageing of the Body

Any discussion of the ageing of individual cells must of necessity be very incomplete. It would also be lamentably lacking in orientation and perspective if they were considered simply as cells only at one period in the age of the body and not as changing members of a changing cellular community of great complexity. The individual is profoundly influenced by the community on the cellular as well as on the human level. The lives of some cells begin not later than when the body is one year old and extend until it dies. For them the changing community influence is almost coextensive with the life of the community. Others, having shorter lives, are subjected to the community during its youth, maturity or senility and even for much shorter intervals. Consequently it is possible, even probable, that individual cells of the same sort will live somewhat different lives, depending upon the period of their existence in the body.

Changing cellular population

The contribution to the population of the four large categories of cells described at the beginning of this chapter changes in very definite ways. But it is feasible here to discuss only the alterations in broad outline omitting details.

For the first few days the intermitotics make up practically the whole embryo. In maturity, and particularly in old age, the postmitotics dominate the picture. Many reverting postmitotics (hepatic, renal, thyroid, parathyroid and other cells) have lost the backing of vegetative intermitotics from which they sprang. They must carry on till the end with occasional mitotic division. The fixed postmitotics (nerve, skeletal muscle cells, etc.) are in a similar position except that mitosis is no longer possible. In the case of some of them the number of survivors suffers a decline with the increasing weight of years. It is not clear whether those remaining have to bear an increasing functional strain sufficient to alter their manner of life; because an excess in number is provided to begin with as a safety factor. Other postmitotics, whose lives are distinctly more hazardous and therefore much shorter (epidermal cells, blood cells, spermatozoa and so on), must be repeatedly replaced. They stem, through intervening differentiating intermitotics, from streams of vegetative intermitotics almost always strategically situated close to the circulating blood. The undifferentiated cells making up these streams usually remain productive of short-lived postmitotics until the death of the body. But the demand for some postmitotics (cf. sperms) decreases in which case the streams become sluggish and may even be entirely arrested.

Occurrence in some part of the body of *misfit cells* is so common a phenomenon as to be reckoned as normal. They lag behind and do not participate as they should in

community structure and function. To characterize them and to explain their habits of life is one of the most complicated of medical problems. Cells of this kind are likely to be set apart where in development cell masses normally come together or separate as at the branchial clefts and where there is displacement of tissue as in the course of the hypophyseal, thyroglossal and Wolffian ducts. The migrations of primordial sex cells are particularly significant. They have been investigated by Swift (1914) and others. Those that do not "reach their normal haven in the sex glands" can be a source of many extra genital teratomata (Ewing, 1940). Tumors of this sort are composed of tissues and even of organs derived from more than one germ layer. Such misfit cells of whatever source constitute a hazard which is greater the more primitive they happen to be and *pari passu* the wider their developmental potencies. But only a small minority make themselves known by tumor formation. How long they may live individually or in series immune to processes of ageing in the body as a whole is a fascinating problem.

Changing fluid environment

According to Lowry and Hastings (Chapter 5) the available evidence suggests that during growth there is a relative increase in the proportion of cells and a resulting decrease in extracellular fluid. By "extracellular fluid" they mean tissue fluid plus lymph but without blood. In ageing, the downswing of the curve, they find that conditions are reversed, that there is a relative decrease in cells and an increase in extracellular fluid.

A difference of opinion exists as to the degree of uniformity in composition of extracellular fluid. Lowry and Hastings admit the possibility of slight local differences but regard it as essentially the same throughout the body. Cowdry on the other hand is impressed by certain local differences in tissue fluids (extracellular fluid minus lymph) which have been established (Chapter 2) and expects that others will be brought to light. It is safe, he believes, to assume that certain of these fluid environments of cells change with age not only in volume, as Lowry and Hastings claim, but also in character. The factors involved in both quantitative and qualitative alterations include exchange through vascular and lymphatic endothelia and the cell membranes of tissue cells. Since some tissues are without blood capillaries, others are devoid of lymphatics and their cellular inhabitants are of many sorts, many possible differentials are created.

Space only permits brief reference to the blood in this connection. Because the ageing of blood vessels is often regional, slow in one area and fast in another, the resulting alterations in the volumes of blood delivered are likely to be uneven. The combined capillary endothelial surface, ordinarily about 6300 square meters (Krogh), probably decreases in extent after maturity with age. How it changes in quality is unknown. Some hypothecate a general decrease in permeability and others an increase. Certain parts may remain unchanged; for, as long as life of the body endures, some capillaries can sprout new capillaries. In the capillary bed, and fre-

quently between it and epithelial cells, muscle cells and others, is connective tissue. As a rule this changes in quality and in amount with age (fibrosis) and hyalinization may (Loeb, Suntzeff and Burns, 1939) again be more in some regions than in others, which may impede the exchange of fluids and interfere with nutrition.

It is within the tissue fluid environments that hormones act on the cells. If these were restricted to the blood stream they would not be effective. With growth of the body the interplay of hormones increases in number of actors and in tempo. It soon reaches a maximum which is maintained for a time and then falls off irregularly. Loeb (1941) and his colleagues have shown "that hormones are able to accelerate or intensify some old age changes and to retard or reverse certain others, and that the same hormone may induce both these effects under varying conditions. But it has also become evident that these effects of hormones are limited by the inherited constitution of the living substratum, and that they cannot accomplish much more than to spur on or to inhibit tendencies which are preformed in the stratum on which they act." In some respects, therefore, the tissue fluid environments of the cells whose lives begin and end during the youth of the body are different from those of others of the same type whose existence happens to be during senility.

Unfolding of hereditary traits

That these are not all manifested simultaneously at a particular age is common knowledge. Consequently cells of a given type, existing in the early life of the body may escape the results of an hereditary influence which makes its appearance later in life through modifications in the cells of the same kind that follow them. The clearest examples are to be found in experiments with closely inbred strains of mice. The Silberbergs (1941) have discovered that skeletal ageing appears at very definite ages in different strains so that the timing of the unfolding of hereditary traits determines the period of immunity of the cells in question to the otherwise almost dominating influence of heredity. Their lives are evidently different in the several strains depending on whether they come in upstanding youth, vigorous maturity or failing old age of the body.

The waning of special functions

Not merely the shifting cellular population, the changing fluid environments and the impact of hereditary forces but factors too numerous to mention influence the lives of cells in the ever changing body. As feebleness approaches functional alterations obtrude themselves. These are the collective expressions of modifications in myriads of cells and also in fibrous components that must not be forgotten. Several chapters in this book

contain clues which if followed up may reveal differences in the ageing of individual cells of the same variety at different periods in our lives.

For instance, MacNider has found (Chapter 4) that the adaptability of cells of the kidney and liver decreases so that it becomes more difficult to protect them against poisons. To put it differently, their susceptibility increases and they even come to look different. But the epithelial cells of these organs, especially those of the kidney, are long lived and it is consequently not easy to tell whether the change takes place within the compass of individual cell lives or in the lives of a succession of cells of the same variety.

The responsiveness of the testicular interstitial cells of young rats and monkeys to the gonadotropic hormone decreases in old animals (Engle, Chapter 27). Here the probability is greater that the cells in the older animals are not the same ones as in the younger animals, that there is a true change in individual cell life with ageing of the body. "Viability tests" indicate that the sperms produced in advanced years differ from those formed in the vigor of youth.

Masters refers to the loss of reactivity of the uterus with advancing age (Chapter 25). As far as this involves the surface epithelium, it is evident that the individual cells in old women are removed by many generations from those earlier in life because of the repeated loss of cells in menstruation.

Reference has been made under ageing of individual nerve cells to resistance to virus infections. Duran-Reynals (1940) has found that parallel with the growth and ageing of individual fowls there develops in the blood an antibody-like factor endowed with the property of pronouncedly suppressing the effects of several viruses. He thinks it more likely that these natural antibodies are serological manifestations of ageing than the results of subclinical infections. The question for us is whether the individual cells concerned exist in early life without producing the antibodies and whether later on other cells of the same type do so and in doing so live somewhat different lives.

Schultz (1934) has discovered that the major increase in reactivity of rabbits to horse serum is in the phase of sexual maturation. In trypanosome infections of rats Kolodny (1940) has observed, in confirmation of Schultz, that "The period of maximum immunological activity occurs concomitantly with the onset of physiological maturity." We wish to know whether cells producing antibodies in this period of life of the body are more numerous or whether they differ in their individual lives by enhanced function of antibody formation at this time. An unlikely explanation is that the same individual cells are so long lived that they function throughout the life span.

It has been discovered that epidermal cells of the embryo undergo a

profound alteration at or before birth. Their intranuclear viscosity increases suddenly (Cowdry and Paletta, 1941) and their properties cannot fail to be modified thereby. Later on crops of new epidermal cells, whose whole lives in series are well ordered for years, take their places. But as the body grows old, a remarkable instability appears as between different groups of cells or the same sort. This is manifested by local epidermal atrophy and hyperplasia and by local pigmentation and depigmentation. MacCardle[1] has recently found local increase and decrease in mineral constituents. About the same time there occurs in the individual lives of these cells a hazard, which before had been almost negligible, namely, the possibility of transformation into malignant cancer cells which are less responsive to community control and whose behavior is almost a law unto themselves. Many other sorts of cells have a similar hazard which sometimes is maximum for each at a distinctive period in bodily ageing and is *partly hereditary, at least in mice in which tumor incidence is often very* different in different genetic strains.

Onset of malignancy

To accurately date the malignant change is well-nigh impossible because malignancy is a kind of behavior and the cells about to become malignant cannot be continually watched.

Whether the malignant change can take place at several age levels in representatives of the same type of cell is questionable. There is a chance that in some cases the change may be gradual, or it may be sudden, yet *lead slowly to the distinctive behavior that* calls *attention to it.* Thus in mice, the skins of which are treated with a cancer provoking substance, the malignant change may be so long delayed after the last application as to make it highly probable that during the interval the cellular population of the epidermis has been replaced not once but several times by the production of successive generations of cells. Perhaps, only the ancestors of the cells which become malignant were directly influenced by the substance in question. Cancer develops slowly in long lived humans and rapidly in short lived mice. In both it is about the same fraction of the average life. Does this mean that the cells of each generation that passes during the *period live longer in humans than in mice*, or that the length of cell life is about the same in humans and mice but that in humans there are more generations of cells?

Carrel (1925) has stated that "the malignant monocyte differs from the normal one chiefly because it is a diseased cell which is short lived." More recently Fischer (1937) has expressed the same view of the shortness of life of malignant cells. To actually measure their length of life is just as

[1] Personal communication, Dr. R. C. MacCardle, National Cancer Institute

difficult as for normal cells. A direct comparison of the two under similar conditions cannot be made because in their blood supply and their ability to get along with less oxygen the malignant cells differ from normal cells. Tumor cells certainly live both intermitotic and postmitotic lives. The intermitotic lives predominate, especially in a rapidly growing tumor. These are generally short with but little structural differentiation and few signs of ageing. Nevertheless, intermitotic lives may be fairly long because malignant tumors occasionally have quiescent periods of considerable length. The postmitotic lives are quite different from the intermitotic, end with death and may exhibit processes of ageing, like keratinization, which resemble more or less those of normal cells of the same type. In other cases cancer cells die *en masse* and perhaps more quickly than their normal prototypes. According to Ewing (1928), tumor cells "suffer the same degenerative changes as normal tissue."

Whether a cell once made malignant can revert to normality is as difficult to ascertain as whether a normal cell can in its individual life become young again. It is admitted that *groups* of normal cells can dedifferentiate. It is generally assumed that, on the contrary, the malignant change is irreversible, that all the descendants of malignant cells are also malignant. Close examination of this doctrine brings out the need for qualification. Some are and some are not malignant (or at least do not remain so). Obviously those cells that live postmitotic lives are not malignant when malignancy is measured by comparatively unregulated multiplication, by invasion of other tissues or by both. In a squamous cell carcinoma with many epithelial pearls a considerable proportion of the cancer cells have by differentiation, or ageing, lost their malignancy. The malignancy is carried on not through them for they die, but through lives of intermitotic cells. Yet it would be difficult to prove that *all* intermitotic cell life in a cancer is malignant because the possibility cannot be excluded that some nonmalignant intermitotic cells are formed but cannot survive in series in competition with their malignant neighbors.

The forces capable of bringing about the malignant modification are many and varied. They include sex hormones, aniline dyes, hydrocarbons, ultraviolet light, x-ray, radium, perhaps even single mechanical traumata and viruses. It is possible that, though the forces are different, they may act with different degrees of directness on several processes, perhaps in series, and may ultimately deliver the same sort of kick to the previously normal cells. Or the kick may be different while the cellular mechanism influenced thereby may be the same. The cellular mechanism thrown into or out of gear may through operation or lack of operation in the same cell, but more probably in a series of generations of cells, perhaps in a cumula-

tive way, itself condition malignant behavior or bring about other changes which result in malignancy.[2]

After a careful review of available evidence, a Committee appointed by Surgeon General Parran (Bayne-Jones *et al.*, 1938) reported: "that malignancy is a universal cell potentiality." Justification for this statement depends on the meaning attached to the words "cell" and "malignancy." Protozoa, bacteria and rickettsia are cells yet we do not think of them as possessing the potentiality of malignancy. The abnormal paramecia, which Mottram (1941) has produced by treatment with carcinogens, are certainly interesting. Further data on their resemblance or lack of resemblance to cancer cells will be eagerly awaited. A report by Spencer and Melroy (1940) on the influence of methylcholanthrene on paramecia looks promising. If Green's idea (1935) is accepted, some viruses may be cells, which, owing to parasitism, have lost most of their properties except multiplication. Many examples can be cited of gradual and sudden changes in viruses involving great increase in virulence but whether these are at all analogous to malignant alterations in cells is very questionable. Among plants the cells of a few species may grow and produce tumor like masses but their behavior is not malignant in the sense that human cancer cells are malignant. The assumption, that, if the whole range of multicellular animals were examined with sufficient thoroughness, cases of malignancy would be found in every cell type proving that it is for all of them a universal cell potentiality, is unwarranted.

For any single species, *homo sapiens* for instance, observations of malignancy are so few in contrast with the multitude of cell types as to place the burden of proof on those that make the statement despite its further limitation to cells capable of division which may have been intended. Search for exceptions has been desultory because people are more interested in the malignant change than in its absence. However, no cases have been reported of neoplastic proliferation of the epithelium of the ductus deferens (Thompson, 1936) and Ewing, in his classic, does not mention cancers of the semicircular canals, utriculus and sacculus of the inner ear. Moreover the period of intrauterine life has been somewhat ignored. All the tissues of the embryo and fetus are not young and vigorous. They do not develop evenly with no signs of ageing, atrophy and death. Ontogeny partly repeats phylogeny. The pronephros is succeeded by the mesonephros and this in turn by the metanephros. The fetal cortex of the adrenal wastes away. Details are given by Benner (1940). Great veins become fibrous

[2] The frequently expressed idea that some cancers, using the word in its broad sense, may arise from "embryonic rests" is not ignored. Such misfit cells have already been mentioned.

cords or entirely disappear. In the changing population it is possible that many types of cells live their lives without ever becoming malignant, that for them malignancy is *not* a universal cell potentiality.

When ultimately all the types of cells that make up the body at different ages can be arranged in sequences, beginning with those of highest potentiality of malignancy and extending to others never known to exhibit malignancy, an opportunity will be afforded to identify the conditions that make the potentiality, if it exists, a reality on the one hand and that hold it in abeyance on the other.

The realization of the potentiality for malignancy is apt to occur with greatest frequency in certain decades which depend to some extent upon the cell type involved. For cells of short lives those in existence at the time of greatest frequency of the malignant change may perhaps differ in quality from others before this critical period sets in. Thus mammary gland cells at the period of highest incidence of breast carcinoma may differ from their antecedent cells earlier in life. The same can be said for cells of the testicle. The lack of uniformity or instability of epidermal cells in people past middle life has been noted. A bodily age differential is thus created. Other age differentials have been alluded to. Thus, cells of some types live free and easy lives while their descendents alone feel the grip of hereditary traits. Some tissue fluids change with ageing of the body. It is not reasonable to suppose that the cellular inhabitants are uninfluenced thereby. Consequently any account of the ageing of short-lived individual cells of a particular sort will be incomplete if it relates only to a single period in the life of the body.

Summary

On the basis of the lives that they live most cells of the body can be roughly divided in four great classes.

1. At the bottom of the ladder of differentiation are the *vegetative intermitotics*. For them individual existence begins with their formation by mitosis and ends with the next following mitosis when each gives rise to two new individuals. Basal cells of the epidermis, primordial blood cells, and spermatogonia are good representatives of this class. Age changes are minimum because individual cell lives are short and do not include either a detectable increase in structural differentiation related to the acquisition of specific function or a downswing of vitality preliminary to death.

2. The *differentiating intermitotics* spring from the streams of vegetative ones through the development by some of their daughter cells of specialized properties. It is typical of differentiating intermitotics that each cell is a little more specialized that its parent, whereas in the basic, vegetative

intermitotic lines each cell resembles its parent. This differentiation is inherited so that specialization in the series of individual cells is step-like. Thus, hemoglobin increases in erythroblasts and normoblasts, and specific granules in myeloblasts and myelocytes. In order to persist, lines of differentiating intermitotics must be continually replenished by the appearance of new lines of cells from the vegetative intermitotic streams. Otherwise they would differentiate themselves out of existence; for, with the passage of each generation, the cells living at the time would become further removed in their properties from the original vegetative intermitotics with none to take their places. The individual lives of differentiating intermitotics are like those of the vegetative ones insofar that there is no phase of senility terminating in death. As in the case of the vegetative intermitotics individual life ends for each by mitosis and the production of two other individuals. Age changes are likewise inconspicuous but in their lives differentiation advances which does not happen with the vegetative intermitotics.

3. The *reverting postmitotic* cells are in sharp contrast. They are on a plane higher than the differentiating intermitotics because each individual cell possesses the differentiation necessary for its specific function or functions. Many of them age and die without descendants but they can, when the need for more cells is great, stop the process of ageing, divide, and produce two cells to take their places. That is to say, they can revert to an intermitotic existence. Such cells in the liver, kidney, thyroid and other organs are long lived. A factor of safety is provided by their presence in large numbers. The series of differentiating intermitotics, which led up to them in early life of the body, are often soon dispensed with, though some carry on until the last. In the individual lives of reverting postmitotics ageing will, of course, be most manifest in those that become senile and die. The changes are conditioned to some extent by the type. They have not been much studied.

4. The *fixed postmitotics* are so highly differentiated that in the phase of specialized function they are not, like the reverting postmitotics, capable of division. In consequence, all of them exhibit the downswing of vital activities leading inevitably to senility and death. The short lived ones (erythrocytes, neutrophilic leukocytes and so on) are backed by lines of differentiating intermitotics, leading from the vegetative intermitotics, by which are provided new cells to function in their stead. Long lived ones (nerve cells, cardiac and skeletal muscle cells, etc.), on the contrary, lose this backing at an early stage in the life of the body. But the safety factor of great numerical excess, combined with a characteristic tenacity of individual life, enables many to continue in service, though a considerable number die by the wayside. These are the cells in which age changes have

been mainly investigated. Each kind is possessed of characteristic structure and function so that the changes for each will be different. No underlying process (or processes) of ageing common to all has been discovered. √ The lives of all cells are conditioned by heredity and environment. A great deal depends upon the quality of the fertilized egg from which they originate. This may be expressed in countless ways. The most evident is *the presence or absence of a characteristic vigor, or tenacity of life, in the whole body or in some of its parts.* Throughout their lives cells must adjust themselves to their fluid environments. Evidence is accumulating that these change, as the body ages, some more than others and perhaps in different ways (Chapter 2). With decline in old age there is a progressive decrease in the number of fully differentiated cells of certain categories, but it is not known whether this is any particular hardship on the remainder though a hazard is created because the numerical margin of safety is consumed. Individual cell lives, for members of the same type, may differ in youth, maturity and old age of the body. One of these differences is in the extent of exposure to the tendency of malignant transformation.

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4

AGEING PROCESS CONSIDERED IN RELATION TO TISSUE SUSCEPTIBILITY AND RESISTANCE

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Hardly an aspect of ageing is of more importance than changes in tissue susceptibility and resistance. As Cannon has explained in Chapter 22 (2nd ed.), an aged person suffers more both from heat and from cold than one in the prime of life. Failing adaptability may have a direct relation to change in tissue susceptibility. Susceptibility to certain diseases increases with age and to others it apparently decreases. To investigate such basic phenomena in human beings is obviously very difficult. A shift to animals in which the experiments can be thoroughly controlled is indicated.

During the past thirty years a large number of animals (dogs) have been used in this laboratory for purposes of investigation. Fortunately, in one of *the early series of experiments (4) the factor of the age of the animal* appeared to exert a definite influence on the type of reaction manifested by the members of the group. Since this time a record has been kept of the age of all animals used for experimental purposes. In some instances such a record is of doubtful accuracy and has been so interpreted. However, a continuous record is available of at least one factor, that of age, which may exert an influence over a variety of reactions occurring in such animals whether these be expressed locally in an organ, indicating cytological susceptibility or resistance, or whether the reactions may be of a more generalized order as shown by disturbances in the stabilization of the acid-base equilibrium of the blood. The present study is based on an analysis of the factor of age as expressed by dogs reacting to a variety of experimental procedures. The animals under review were either bred in the laboratory kennels, in which case the age record is accurate, or were ob-

tained from other reliable sources, in which case the record is relatively accurate with an assured discrepancy of only a few months. These dogs may be divided into three groups: an immature or young group, varying in age from puppies 6 weeks old to animals of 1 year of age; the adult group, dogs between 2 years and 7 years of age; and a senescent group of animals varying in age from 7 years to 14 years and 4 months. Such a grouping is sufficiently elastic to permit the factor of age to express itself as a part of the response of such animals to various injurious agents, which damage may or may not be followed by such cell changes as to develop a resistance on the part of such tissues to subsequent injury. There is, however, a variable which should be stated. The animals under consideration were of different breeds and mixed breeds. Such factors may influence the rate with which the ageing process develops.

Susceptibility of the Kidney of Ageing Animals to Uranium Nitrate, Ether and Chloroform

The susceptibility of the kidney to the action of uranium as influenced by the age of the animal is beset by the difficulty that as the animal ages certain changes may take place in the vascular tissue which, whether they be regarded up to a certain stage as an ageing process or as disease, influence by modifying the circulation through the kidney the specific epithelial response to this poison. On the other hand, the fact that the salts of uranium have a selective affinity for the cells in the proximal convoluted segment of the tubule enables one to observe the type and extent of the injury which such a substance may effect as animals age and the influence of age as expressed by the severity of the injury on the type of epithelial repair process which develops both in terms of cell morphology and resistance. It would be fortunate in considering the relative toxicity of uranium nitrate in the animals of the three age groups if definite cytological differences could be determined to exist in such cells which were dependent upon the age of the animals. Except for certain animals in the senescent group of dogs such differences although suggestive are probably too ill-defined to be of any determining significance. In the senescent animals referred to, a very definite cytological change develops in the epithelium of this segment of the tubule which imparts to it resistance against an amount of uranium which is cytotoxic for normal cells found in this segment of the tubule in adult animals. Such kidneys would appear to fall in that group of renal modifications definitely associated with senescence discussed by Kaufman (3). In so far as differences in the cytological structure of the epithelium in the proximal convoluted tubules are concerned in the young or immature and adult group of animals, it becomes difficult to make any accurate statement. This in turn affords an opportunity for

research. From a histological study of a very large number of kidneys in such groups of animals my impression is that in the immature group the epithelium in the convoluted segment is more flattened and shows less differentiation than in the adult group. In the younger animals the brush border of these cells is imperfectly developed and they fail to show stainable lipoid material in the cytoplasm. In the adult group, cell differentiation is usually clean cut, the cells are higher, even columnar in configuration, and the brush border is well defined. Lipoid material as dust-like particles or small droplets can usually be demonstrated in the cell cytoplasm.

When animals in these respective age groups are intoxicated by uranium nitrate (5, 7) in the amount of 2 to 4 mg. per kilogram, the factor of the age of the animal is shown as a local reaction in the kidney and as a more generalized reaction. The convoluted tubule injury in the young and immature animals is slight when compared with the changes observed in the adult animals and in a certain number of the senescent group. The changes in the younger group consist of cloudy swelling of the epithelium, the appearance of stainable lipoid material, a moderate grade of edema, faulty staining of the nuclei, and rarely any extensive necrosis. The repair process which develops in these young animals results in the formation of a normal type of epithelial cell which fails to have any acquired resistance to secondary intoxications by uranium (12). The relatively resistant epithelium of the younger animals appears to be insufficiently injured by the poison to develop in the repair process a cell of such an altered order both morphologically and chemically as to acquire resistance. When adult animals and a certain number of the senescent group which show a greater degree of specialization in cell structure are intoxicated by the same amount of uranium per kilogram, the same general type of epithelial injury develops but it is of a severer order. Their cells become vacuolated and necrotic, the nuclei are fragmented or appear as shadows, and stainable lipoid material as droplets or fused masses makes its appearance in the cytoplasm of the cells which are sufficiently preserved. The repair process which develops in such animals is characterized by the formation of a flattened, atypical type of cell or by the formation of definite syncytial structures. This type of repair process in the older animals which have participated in a severer type of epithelial injury has a marked degree of resistance to an increased amount of uranium. Apparently the age of the animal not only expresses itself in the degree of epithelial injury but also in the type of repair process which is instituted by the animal. If this repair process is effected by an order of cell which shows poor cell differentiation, syncytial formation, or epithelium of an embryonic type, such tissue acquires a resistance to subsequent injury.

In the senescent group of animals two types of epithelial reaction develop

from the use of uranium. The usual response is characterized by such extensive necrosis and sloughing of the epithelium in the tubules that the institution of any form of repair process becomes impossible. Animals thus affected fail to survive. In another group of such animals there has occurred, as a result of the ageing process or definitely attributable to glomerular disease, the formation of the same atypical type of cell which has been described as the usual process of repair for the adult group of animals. When this type of cell predominates in the convoluted segment of the tubule they have been shown to be resistant to secondary intoxications by uranium. This type of cell or syncytial structure when produced as a reaction of repair from uranium has been furthermore shown to be resistant to bichloride of mercury (18).

The foregoing observations would indicate that there exists a resistance to uranium on the part of the epithelium in the proximal convoluted segment of the nephron in puppies and young animals, and furthermore, that an injury of the order of severity which is induced in such animals by this substance is followed by a process of repair in which cells normal for this segment are formed and which fail to have any acquired resistance to this poison in excess of their natural resistance. In contrast to this type of response the epithelium in the same location of the tubule in older animals shows the ageing process of the animal by an increased susceptibility to the toxic action of this poison which is followed usually by an atypical type of epithelial repair, resembling in certain particulars epithelium of an embryonic nature, which is resistant to uranium. In a final group of senescent animals the epithelium shows such a susceptibility to this substance that a repair process of any kind fails to develop. However, falling in this group of senescent animals there are instances of resistance on the part of the epithelium to uranium in which the cells in the convoluted segment have either changed their morphology as a result of ageing to the atypical type of cell or the change has been induced as a result of disease manifesting itself as a major tissue reaction in the glomeruli.

Reference has been made to a difference in the general reaction of these animals of different age groups to an intoxication by uranium nitrate, a reference which on the basis of its type might be considered of a metabolic nature. The animals as a whole, regardless of the age grouping, become polyuric; there is a loss in weight, a reduction in the reserve alkali of the blood, and the urine contains both albumin and glucose. In addition to these changes, the older members of the younger group of dogs, the adult and senile groups exhibit ketone bodies in the urine. The percentage concentration of these bodies in the urine increases with the age of the animal as does the degree of the disturbance in the acid-base equilibrium of the blood. The composite effect resembles the reaction which may be

obtained in animals from the use of a cyanide, the action of which is to inhibit intracellular oxidations. Arguing from these observations with no ascertained facts for the basis of the argument, one might infer that youthful tissue has a greater oxidizing capacity than senescent tissue and that the same degree of inhibition of tissue oxidations in youthful animals by uranium would find less expression in terms of the hyperglycemia, ketone body formation and in the reduction of the reserve alkali of the blood than would be the case in the adult and senescent group of animals. Such an hypothesis may apply to processes of intracellular oxidations in the epithelium of the proximal segment of the convoluted tubules. Such thoughts are rather closely connected with the differences in metabolic rate in youth and senility as have been observed by Aub and Du Bois (1) and by Du Bois (2).

The significance of the ageing process in animals intoxicated by uranium nitrate is also seen when an attempt is made to protect animals of different ages against the toxic action of this poison by giving intravenously a solution of sodium carbonate (6). When such solutions are employed, the degree of protection which the animals develop both as a local reaction in the kidney and as shown by the general reaction on the part of the animal depends very definitely on the age factor. As the animals advance in years the degree of protection lessens so that in the majority of the senescent animals such solutions are entirely ineffective. The degree to which protection can be influenced is associated very definitely with the ability of such a solution to stabilize and maintain a normal acid-base equilibrium of the blood. This becomes more difficult as the animals advance in years. The animals of the various age groups as normal animals are able to stabilize and maintain this fundamental equilibrium, but when it becomes subjected to the strain of an intoxicant such as uranium, the factor of age shows itself by the older animals giving evidence of a more ready disturbance in the balance and a greater degree of reduction in the equilibrium than is the case with the younger animals. As definite as is the influence of the ageing process on both the readiness and extent to which the acid-base equilibrium of the blood may be interfered with by the use of uranium nitrate, it must be recalled that the injury to both the liver and the kidney in such animals by uranium may in part explain the susceptibility of this balance to such an interference. It would there- [illegible] that the acid-base equilibrium of the blood [illegible] is in a youthful [illegible] animals at different age periods under the influence of some physiological process in which neither the liver nor the kidney participate in an injury.

Extending over a period of ten years, 73 pregnant dogs of different age

periods and at different stages of the gestation period have been studied in this laboratory (9, 11). These animals have varied in age from 11 months to 10 years and 4 months and the duration of gestation from three to ten weeks. The average length of gestation in the dog is nine weeks. Studies of these pregnant animals have been controlled by observations on a group of animals of the same relative age which were not pregnant. In both groups studies of the urine and the use of renal functional tests gave no evidence of renal injury. A study of the normal animals from periods of youth into senescence has shown that these animals are able to maintain a normal acid-base balance of the blood. This does not mean that the balance is perfectly stabilized for in 2 of the older animals in which there was no evidence of renal disease there occurred such variations in the reserve alkali of the blood as to indicate very clearly a lack of stability in this equilibrium.

Studies of the stability of this equilibrium as influenced by the ageing process and the duration of the gestation period demonstrate that the young animals tend to maintain a normal acid-base equilibrium of the blood during and to the termination of the gestation period. As the animals in this state advance in years there is a progressive tendency for a larger number to show an instability of the equilibrium, and furthermore, a reduction in the reserve alkali of the blood occurs earlier in the gestation period in the older than it does in the younger animals. These observations on the influence of the ageing process would appear to be of definite importance for they show how such a fundamental equilibrium is not only influenced by ageing but also the effect of a physiological state, gestation, when it is permitted to exercise its influence as the animal ages. Such observations are furthermore strengthened when the influence of a uranium intoxication is studied in such animals of various ages during the gestation period (20). The toxicity of uranium as expressed by its ability to reduce the reserve alkali of the blood and lead to the development of an acid intoxication shows a rather definite parallel with the age of the respective animals and the duration of the period of gestation. As the animals increase in age and as the duration of the gestation period progresses, the ability of uranium to reduce the reserve alkali becomes intensified.

The ageing process, certainly as it expresses itself in advanced senility, has been looked upon as a type of physiological anesthesia becoming a completed process in death. Processes of oxidation, the completeness with which such reactions are accomplished, the degree to which organs and organ systems function show a retardation in the senescent state which may be compared to the influence of such substances as the general anesthetics on tissues in general, as well as to the localization of their influence in various organs. When the general anesthetics, ether or chloroform, are

employed in pregnant animals of different age periods it has been found that the older animals are more susceptible to the action of such anesthetic bodies as is shown by a reduction in the reserve alkali of the blood and that the duration of the gestation period increases this susceptibility. Furthermore, the use of such substances in pregnant animals is more apt to induce, as a local expression of tissue damage, a renal injury as the animal advances in years. Finally, when an attempt is made to protect such animals against either the localized or general toxic expression of these bodies by the use of a solution of glucose, the degree of protection diminishes as the age of the animal advances (10). In those animals in which chloroform was employed as an anesthetic agent, virtually no evidence of protection was obtained in animals of any age period (13). Many years ago it was demonstrated that associated with the ageing process there occurred an increase both in the amount and distribution of stainable lipoid material in renal epithelium (8). The increase of this material with its appearance in the cells of the proximal segment of the convoluted tubule was associated with the ageing process and in turn influenced the susceptibility of this epithelium to the toxic action of both ether and chloroform. Whether or not such a change in the lipoid content of the epithelium takes place during gestation in an exaggerated form, which in turn determines the susceptibility of the epithelium to the general anesthetics and the degree to which such animals can be protected by the use of a solution of glucose, is entirely unknown.

Susceptibility of the Liver of Ageing Animals to Uranium Nitrate and Chloroform

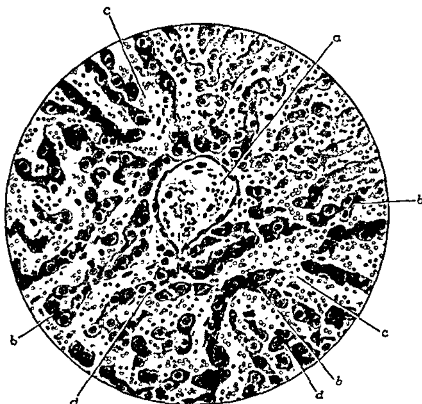
In discussing the ageing process as shown by various changes in the kidney and the influence which such states might have in determining susceptibility or resistance, reference was made to the fact that on account of the specialization in the vascular tissue of the kidney and the susceptibility of this tissue to injury these states might by reflecting their influence on the epithelial tissue interfere with the proper interpretation of the epithelial changes. A difficulty of this sort is not encountered when the liver is studied in an attempt to investigate the ageing process and states of susceptibility or resistance which may appear at such periods or be induced by experimental procedure.

In the liver there is no specialization in structure of the vascular tissue which sets aside a tissue to show evidence of injury, as is the case with the kidney. The liver receiving its blood supply from both the hepatic artery and portal vein, which supplies are united at some point in the liver, afford this organ blood which comes in intimate contact with its epithelial tissue without the intervention of any specialized structure which may influence

ts distribution operating in a physiological manner or under the influence of pathological changes. For these reasons the liver is a more appropriate rgan in which to study the ageing process of its epithelial tissue, the sus- ceptibility of this tissue to injury as influenced by the age of the animal and he development of epithelial changes which may impart resistance to uch tissue.

The observations which have been made on the liver have extended over period of fourteen years, thus enabling such studies to be made on large number of animals at ages varying from 6 months to over 15 years. In these studies the same latitude has been taken in the age grouping s was employed for the dogs in which the ageing process was observed s a localized reaction occurring in the kidney. The animals now under onsideration may be divided into an immature or youthful group with ges varying from 6 months to between 1 and 2 years, an adult group of rom 2 to 8 years old, and a senescent group from 8 years to a few months ver 15 years in age. Histological studies of the livers of animals in the espective age groups made by obtaining biopsy material, except for certain f the senescent animals which will be referred to later, have shown even ess evidence of cytological changes dependent upon age than have similar tudies which were carried out in connection with the kidney. In the very oung animals one gains the impression that cell differentiation in the pithelial cords is less perfect than in the adult animals and certain of the enescent animals. In the young animals stainable lipoid material is dif- icult to demonstrate. It is present as small or coalesced droplets in the dult animals and especially in those senile animals in which a complete hange in the type of epithelium has not occurred. The intoxication by ranium is expressed by a more diffuse and severe degree of epithelial njury in the adult animals and in senescent animals with a normal type of ell than it is by the epithelium of young animals. Following such degrees f injury there develops a difference in the type of repair process. The adult nimals with the severer order of epithelial injury institute a process of epair by the formation of an atypical, flattened type of cell or by cell tructures which are definitely syncytial and which are of functional value n that they can remove phenoltetrachlorphthalein from the plasma and ave acquired a definite resistance to uranium. The very young animals which have shown resistance to uranium repair the epithelial injury by the ormation of a normal type of cell which has no resistance to secondary ntoxications by the poison (15). If those animals of the adult and senescent groups which have effected an epithelial repair by the formation of an typical type of epithelium be subjected to a period of starvation for 24 ours and then be given chloroform by inhalation for a period of $1\frac{1}{2}$ hours, here fails to occur a necrosis of the epithelium around the central veins

of the lobules. When animals with a normal type of epithelial repair process in the liver or adult and senescent animals which have not been subjected to injury and which have an epithelium of the usual order

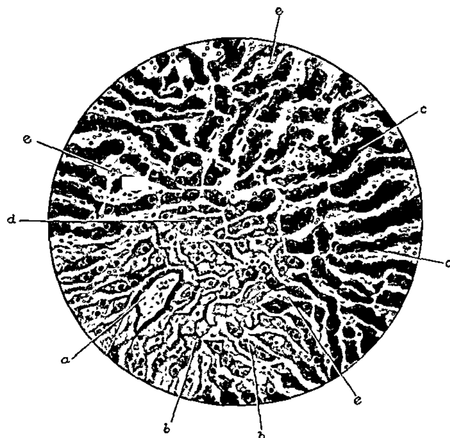


... from the liver of a dog, age 11 years. The liver [illegible] oids appear at c.

are starved for 24 hours and anesthetized with chloroform for 1½ hours, there develops the usual necrosis of the epithelium which involves the inner one-half to two-thirds of the liver lobules (16). The ageing process reflects itself in the liver by an increase in its susceptibility to the toxic action of uranium and by a modification in the type of epithelial repair

process which in turn determines whether or not the livers of such animals have acquired a resistance not only to uranium but also to chloroform.

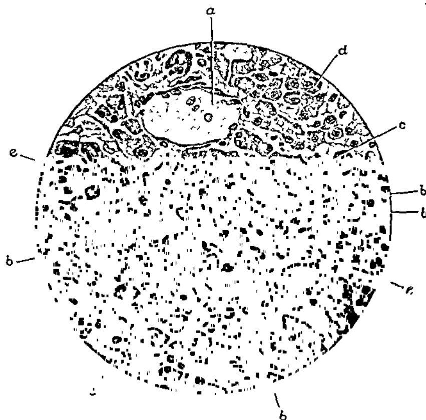
Reference has been made to a group of senescent animals that have



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shown, as a naturally acquired process not dependent upon experimental injury followed by repair, a change in the type of epithelial structure in the liver. Twenty-four senescent animals have been studied in which from some unknown cause but always associated with advanced senescence the type of epithelial structure of the liver has undergone a diffuse change in cell type. Such epithelium occurs as flattened, syncytial cords rarely with

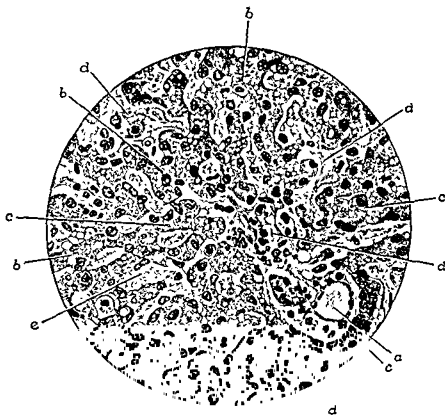
cell differentiation. The cytoplasm of such structures stains evenly and intensely. The nuclei are large in proportion to the surrounding cell cytoplasm and often appear hyperchromatic. Mitotic figures have not been



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observed. Between such syncytial cords are large [illegible] type of epithelium resembles that which develops in [illegible] lowing a severe injury from uranium except that its [illegible] more marked and there is more evidence of [illegible] budding. The naturally acquired, atypical epithelium [illegible]

observed in senescent animals shows an even greater degree of resistance to chloroform than the atypical cells and syncytia which have developed



as a repair process secondary to a severe injury from uranium (17). Such epithelium may be injured by chloroform when its administration is prolonged for 3½ hours. The atypical epithelium occurring in the senescent animals is of definite functional value.

A final group of animals should be discussed not on the basis of the age

of the animals but for the purpose of illustrating how changes in cell types in the liver of the same animal may be associated with states of resistance or susceptibility at different periods of observation. The livers of such adult animals were severely injured by uranium nitrate. The repair process, as was shown by a study of biopsy material, was effected by the formation of the atypical type of epithelial structure which has been described. At this period of observation the liver was resistant to chloroform when given by inhalation for 1½ hours. It failed to induce a central necrosis of the lobules. Two years later than this a study of biopsy material from the liver showed in areas a reversion of the flattened, atypical type of cell to a normal cell of polyhedral contour. At such a period of cell type change, the inhalation of chloroform for 1½ hours induced a partial necrosis in those areas composed of cells of a normal order. The atypical cells remained resistant.

These experiments not only serve to emphasize variations in susceptibility and resistance associated with different cell types and an assumed difference in chemical constitution but also the significance of the time factor in such cellular transitions (19).

Summary

In the preceding analysis of a rather wide variety of experiments in which the age factor has been taken into consideration, an attempt with a fair degree of accuracy has been made to ascertain how the process of ageing expresses itself in terms of susceptibility to injury on the part of organs and certain specialized cells in them, the influence of the same factor as expressed by an organ in acquiring a fixed cell tissue resistance and, finally, certain more generalized reactions on the part of the organism as a whole which are modified by the ageing process. In summarizing the results, the following conclusions would appear to be warranted, ever remembering that the age groupings of the animals were of an elastic order and that the breed of the animals, if pure, as well as the mixed breed status of other animals, might influence not only the rapidity but the extent to which the ageing process develops.

1. Young animals, in which epithelial differentiation may be imperfect and in which epithelial specializations in structure have failed to appear in a state of perfect development, appear to be more resistant to injurious agencies than those possessing a type of epithelium which is perfected in its differentiation and specialization of structure, as represented by an adult group of animals. The occurrence of stainable lipoid material in such cells influences in a favorable manner their susceptibility to injury.

2. When epithelial tissue in young animals in certain organ locations participates in a process of repair, the type of cell formed is predominantly of a normal order for such location and has no acquired resistance to

injury. When a similar type of injury is produced in the more susceptible adult animal and in senescent animals that retain a normal type of epithelial structure, there is shown by such animals either an inability to participate in any type of repair process or the process is effected by an atypical type of cell resembling in certain respects, especially in its lack of differentiation, embryonic epithelium which, though of functional value, has acquired a resistance to injury. It would appear that in adult and certain senescent animals the power of instituting a normal type of repair for epithelium in certain locations has been modified or lost, and that the difference in the readiness with which repair is effected and the type of cell employed in the process is associated with the age of the animal more than it is with the severity of the injury in the animals of the different age groups. As an animal advances in its life span, the cytology of the repair process becomes modified and associated with such changes there may develop an acquired resistance for certain chemical substances. This is especially true both for the kidney and the liver in animals in advanced senility in which a type of abnormal epithelium may appear either as a result of the ageing process or may be produced as a reaction of repair in the senile state which is resistant to injury and, though of less functional value, tends for a period to stabilize the animal as a senescent animal and protect these organs against an extension of injury. The experiments would indicate the significance of time expressed as ageing in not only influencing cell susceptibility but also the ability of certain tissues to so modify their process of cell repair as to acquire resistance. Such a resistance acquired as a result of ageing or as a result of artificial injury followed by repair is of changing order. Resistant cells may so change their morphology and likely at the same time so modify their chemical structure that susceptibility to injury again develops. These observations emphasize the changing, shifting character of even fixed cells. They have been of a very gross order. Changes of a finer nature, impossible or difficult at present to detect, when accompanied by chemical modifications may explain in part not only the ageing process but also the susceptibility and resistance of fixed cells at various age periods to the effect of outside agencies and to chemical bodies produced in cells as products of the life process.

3. An observation of significance in connection with the ageing process and which does not confine itself to one organ or group of organs is the effect of age on the stability of a fundamental equilibrium in the organism, the acid-base equilibrium of the blood and tissue juices. As normal animals advance in age this equilibrium becomes of an unstable order and in advanced senility the organism may be unable to maintain it within the range of normal variations. Such an instability may be demonstrated when animals of different ages participate in the physiological process of

gestation and when they react to various intoxications. Furthermore, it becomes increasingly difficult as the age of the animal advances to restore to the normal as well as to stabilize this fundamental equilibrium. A tendency to, or the actual development of, a reduction in the reserve alkali of the blood as the animal ages appears to be a definite characteristic of the ageing process which, in turn, by influencing chemical reactions of an intracellular nature during life, may in part determine the rate with which the ageing process develops.

The ageing process as shown by various studies which have been reviewed is not one which proceeds from a certain peak of perfection in an uninterrupted downward course to its termination. The process is characterized as it progresses by variations in cell susceptibility and by the development of transitory states of cell resistance which give to the downward progress of the curve, representing ageing, an irregular course; points of depression, indicating periods of susceptibility, and points of elevation in the curve, variable in their duration, at which resistance is acquired. As ageing progresses such transitory states of cell adaptation to it become less and less effective, finally manifesting their inability in terms of such depressed function or lack of function on the part of an organ or organ system that the life of the organism as a whole comes to an end.

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5

QUANTITATIVE HISTOCHEMICAL CHANGES IN AGEING

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The changes occurring during growth and senescence have been at various times considered from at least three different points of view. There are, first of all, descriptions available of certain functional and anatomical alterations with [illegible] the animal considered as a whole. Second, to under-

functional changes observed in whole organs have been attributed to the several tissue components, and attempts have been made to discover what alterations with age have occurred within the cells themselves and in their immediate environment. This last is the histochemical viewpoint. Such an approach includes not only inquiry into the composition and functional capacities of the various tissue phases, but also assumes responsibility for the quantitative measurement of the relative amounts of the various phases. Function may be altered as surely by changes in the amount of functioning cytoplasm as by changes in the metabolic capacity of the individual cells.

In this chapter, it will be the purpose of the authors to restrict their discussion of the chemical changes in tissues with ageing to those data which lend themselves to morphological interpretation. The limited data available for such an interpretation serves to emphasize the need for additional careful quantitative observations of this nature.

INTRODUCTION

Functional relationships between cells and their environment

The tissues of the organism may, for purposes of chemical description, be regarded as composed of differentiated cells, varying in their intracellular

composition, and surrounded by a fluid medium of essentially uniform and constant composition. The intracellular composition of the cells is actively influenced by the enzymic reactions, both hydrolytic and oxidative which occur therein. The composition of the extracellular fluid is passively influenced locally by certain of the chemical reactions of the cells. The composition of the extracellular fluid is, however, relatively constant, and is the result of the integrated and various activities of the component organs making up the physiological system as a whole.

The following example illustrates this relation between tissue and organ reactions In muscle, the intracellular enzymatic reaction of glycogen breakdown may result in the formation of lactic acid. This will, in turn, cause a decrease in intracellular bicarbonate concentration, an increase in intracellular carbon dioxide tension, and an increase in hydrogen ion concentration. The intracellular buffers will, of course, participate in the reaction to diminish the change in intracellular pH. Thus, the changes produced in the intracellular components will include: 1) an increase in acidity, and 2) an increase in the osmolar concentration of intracellular solutes.

Such changes are promptly and effectively minimized by the interchanges which occur between the cell and the extracellular fluid environment. These include 1) the passage of dissolved carbon dioxide into the extracellular fluid to equalize the carbon dioxide tension, 2) the passage of water into the intracellular fluid to equalize the osmotic pressures, 3) the removal of lactate ions by (a) diffusion into the extracellular fluid, and (b) their further use in various reactions of carbohydrate metabolism. This example of the extracellular and intracellular reactions and their ramifications in the breakdown of glycogen serves to illustrate the reasons for considering the complexity and interrelationships within the tissues and organs.

Thus, to understand the ageing process, we need to know not only the changes which occur in the mass and chemical composition of the phases of a tissue, but also those changes which occur in the efficiency with which interrelated organ systems work.

Normal standards of tissue composition

The central problem of the ageing process is the description of the extent to which the tissues and organs of the body undergo changes with the passage of time. It would seem to be highly desirable to have available a histochemical description of the tissues and the chemical changes which they undergo in the absence of specific pathological stimuli. In practice, this may be very difficult to achieve; but just as standards have been obtained for the basal metabolic rates as a function of age, so should it be

possible to obtain measurements of the composition of tissues, both in histological and chemical terms, and measurements of the functional activity of organs and the organism as a whole.

The changes which occur in the first two decades of life are under active investigations by pediatricians and nutritionists. However, the systematic study of the later stages of man's ageing process has been in large measure neglected. Attempts to delay or circumvent the changes which decrease the efficiency of the organism await the chemical and physiological description of the ageing process.

Quantitative Histochemical Method of Approach

Histological versus histochemical description of tissues

The histological examination of tissues of animals of different ages has been widely carried out by numerous investigators over a period of many years. In general, the point of view adopted by the histological observer has been to search for definite and clear-cut evidence of morphological abnormalities. This approach has been of great value in the detection of qualitative changes of a morphological nature which are widespread. There may, of course, be subtle quantitative changes of a structural nature whose presence escapes the eye of the observer. To be able to supplement the histological study of tissues with techniques which permit the quantitative evaluation of changes occurring therein would broaden greatly the value of the morphological approach. This may be considered the purpose of histochemical studies.

Specifically, whereas histological examination emphasizes a qualitative alteration in the morphological makeup of a tissue, histochemical analysis of a tissue emphasizes the quantitative aspect of the problem; and, indeed, gives the hope that even when morphological changes are not detectable, a functional alteration in a tissue may be found to be associated with quantitative histochemical alterations.

Chemical versus histochemical description of tissues

Unfortunately, except in the case of the red cell, it has not proven feasible to analyze the cells of the body directly. The simple separation of blood into cells and serum by centrifugation is not applicable to solid tissues. It has, therefore, been necessary in general to analyze organs without preliminary separation of the cells from the interstitial fluid and connective tissue. Just as variations in the proportion of red cells cause alterations in the hemoglobin content of the blood, so would variations in the proportions of the cells in a tissue affect the observed concentration of any substance which was not evenly distributed throughout each tissue phase. Since each

component of the tissue mosaic has its own specific composition, the analytical figures obtained from a specimen of tissue will represent a weighted average of the composition of the several phases of the sample. Without some basis for the unravelling of these composite data, confusion may arise in the interpretation of gross analytical results. Even marked changes in the observed data may be *only* the reflection of variations in the proportions of phases rather than the sign of changes in the constitution of any given phase. Conversely, the occurrence of actual alterations in the composition of the intracellular phase, for example, may be obscured by changes in the relative amounts of the unlike phases.

The changes occurring during growth can be cited as a case in point. An outstanding feature of early development is an increase, with time, in the proportion of solids in the tissues. If the developing tissue were to be *considered as a homogeneous system as described by the analytical data*, then one would conclude that the enzyme systems were functioning in a progressively drier environment. If, on the other hand, attention were directed to the essentially cellular nature of tissues, it would become evident that the increase in solids during growth might be merely the result of an *increasing proportion of cells*. Were this the case, the intracellular fluid environment of the enzymes would possibly be found to undergo no great change during the growth process. This is, apparently, the usual situation.

The histochemical approach, then, constitutes an attempt to ascertain not only the chemical nature of the entire tissue, but also the chemical constitution of individual tissue phases, and to determine the nature of reactions and developments within the heterogeneous cellular matrix.

The deductive histochemical method

Although here used in a restricted sense, the word *histochemistry* has three different connotations which may be mentioned: 1) the qualitative histological identification or localization of chemical individuals, (Dempsey, Chapter 17); 2) the semiquantitative measurements under the microscope of the local concentrations of various substances in tissue sections (Gersh, (1)); 3) the quantitative measurements of the amount and nature of individual tissue phases either by (a) direct analysis of pure phases (Maurer, (2)), or (b) *rational treatment of composite data to yield information about* histological phases. It is this last *deductive* quantitative histochemical approach which forms the basis of much of the subsequent discussion.

The outline which follows of the histochemical treatment of data has been applied to tissue analyses by numerous investigators: Peters (3); Fenn, Cobb and Marsh (4); Eggleton, Eggleton and Hamilton (5); Hastings and Eichelberger (6); and others. It is of interest that such a possibility

was pointed out as early as 1907 by Urano (7), but his suggestion was lost sight of for many years.

Basis of Calculation. The characteristic of all tissues being that they are composed of cells surrounded by fluid, however small in amount this fluid may be, provides the thesis for the histochemical approach to the problem. The immediate goal in histochemical studies of tissues is to obtain information on: 1) the proportion of extracellular and intracellular phases of the tissues; and 2) the composition of the extra- and intracellular phases. This is a goal which has been reached in some instances but not in others. That is is attainable at all rests on the now generally accepted premise that the extracellular fluid of tissues differs only in a certain few respects from the blood plasma in its chemical composition. Those differences which it does have are: 1) its lower content of soluble proteins, 2) the small, predictable differences in its electrolyte pattern due to the Gibbs-Donnan effect, and 3) its slightly higher carbon dioxide tension and slightly lower pH which results therefrom. Since the plasma is always accessible for analysis, it is, therefore, possible to know the concentration of the ionic constituents of the extracellular fluid.[1]

Suppose, therefore, that there is a constituent of both plasma and of extracellular fluid which is not present in the intracellular phase of tissues. By analyzing a tissue for this constituent, one may then calculate the amount of extracellular fluid in that tissue. This is true for the chloride of skeletal muscle. By determining the concentration of chloride in the blood plasma, one may then estimate the concentration of chloride in the extracellular fluid. By analyzing muscle for its chloride content and dividing the tissue chloride concentration by the concentration of chloride in the extracellular fluid, one obtains a figure for the proportion of extracellular fluid in the tissue.

For example, a specimen of rat muscle was found to contain 10.5 milliequivalents of chloride per kilogram of tissue. The serum of the same rat was observed to have a concentration of 105.2 milliequivalents of chloride per kilogram of serum water. By taking account of the Donnan effect on the chloride distribution, it is possible to calculate that a kilogram

[1] This conventionalized view of extracellular fluid as essentially a serum-ultrafiltrate is, of course, oversimplified. This point is discussed in Chapter 2. The justification for the present simple assumption is that the family of extracellular fluids differing somewhat as they do, nevertheless resemble each other far more closely than they resemble intracellular fluids. The differences that do exist in the nature of the extracellular fluid in various organs are often without consequence for the present type of tissue analysis. Eventually, it should be profitable to consider the differences in various extracellular fluids in order to obtain a second order approximation of the histochemical configurations.

of extracellular fluid in this rat would contain 109.7 milliequivalents of chloride. This sample of rat muscle contained, therefore, $\frac{10.5}{109.7} \times 1000 = 96$ grams of extracellular fluid per kilogram of muscle.

In some tissues, the extracellular phase is made up not simply of fluid, but of fluid plus connective tissue fibers. To obtain the amount of total extracellular phase of tissue, it is necessary to determine the collagen and elastin of the tissue, and to add this to the extracellular fluid in the tissue.

Having determined the extracellular phase of the tissue, the remainder of the tissue may be regarded as the intracellular phase. If the intracellular phase is composed predominantly of one type of cell, as in skeletal muscle or myocardium, the further evaluation of the concentration of intracellular constituents is a simple one. If, on the other hand, the intracellular phase is composed of several types of cells differing in chemical composition, calculations become less certain.

CORRECTIONS FOR BLOOD AND FAT. There is a further aspect of the histochemical approach which must be taken into account. The amount of fat and the amount of blood present in a piece of tissue taken for analysis is by no means uniform from one sample of tissue to another. These extraneous components of the tissue must be removed or allowance made for them in calculating the proportion of extracellular phase. It has been found to be practicable to correct for the fat of the tissue simply by first extracting the dried tissue with fat solvents and making the analyses on the extracted tissue. The amount of blood present in the tissue is estimated by extracting it from fresh tissue and determining the quantity colorimetrically or spectrophotometrically. In other words, for the morphological interpretation of analytical results on tissues, the concentration of constituents should be expressed in terms of units of fat-free, blood-free tissue. Voit (8) observed that fat and lean animals, although differing markedly in total solid content, show approximately the same content of fat-free solids; and Magnus-Levy, as early as 1910, recommended the reporting of tissue data on a fat-free basis.[2]

EVIDENCE FOR EXTRACELLULAR POSITION OF CHLORIDE. In the case of

[2] "Für gewöhnlich geschieht die Umrechnung auf die fetthaltige Trockensubstanz. . . . Ich halte das weder für die Muskeln noch für die anderen Organe, die markhaltigen Nervenfasern ausgenommen, für richtig Zwar gehört zu jedem gesun- [illegible] Hauptmasse nicht als [illegible], sondern ist in Form [illegible] Es ist alsreines Fett [illegible] verschiedene Gehalt [illegible]lich beeinflussen und [illegible] sollte eine Berechnung in der Trockensubstanz nur auf die fettfreie Masse geschehen." (9)

the liver, the histochemical determination of the proportion of extracellular and intracellular phases has been ingeniously compared with a quantitative application of histological methods (Truax, 10): Histological sections of liver were made and photographed and the photographs enlarged. The portions of the photograph which were apparently extracellular were cut out and weighed. By dividing the weight of the cut-out portion by the weight of the original photograph of the whole section, he obtained a figure for the proportion of extracellular material in liver. A histochemical estimate of the extracellular phase of the liver was also made from chloride analyses, and the two estimates were found to be in satisfactory agreement.

The evidence for the extracellular position of chloride in skeletal muscle rests on the following: 1) the direct microscopic studies of Gersh, who found that chloride was exclusively extracellular (11); 2) the perfusion experiments of Amberson, Nash, Mulder and Binns (12), who showed that chloride could be removed without apparently affecting the intracellular phase; 3) the observations of Hastings and Eichelberger (6), who varied the amount of chloride and the acid-base balances of tissues and showed that only by assuming an extracellular position for chloride could their results be accounted for; 4) the experiments of Fenn, Cobb, and March (4), Eggleton, Eggleton and Hamilton (5), and others who showed that isolated tissues equilibrated *in vitro* against solutions of varying chloride concentrations, retained chloride in proportion to the concentration in the medium, but at a very much lower level; and 5) the experiments of Manery and Bale (13), and Manery and Haege (14), who used radioactive sodium, and radioactive chloride, and concluded that in many tissues, for practical purposes, all of the chloride and sodium were outside the cells.

In many tissues, the position of sodium, like chloride, is normally essentially extracellular, and this constituent may also be used to determine the proportion of intra- and extracellular material. It is of interest that Liebig (15) suspected that sodium occupied chiefly an extracellular position, and stated his belief that potassium would prove to be at a much higher concentration in the tissue cells than it appeared to be in the tissue as a whole. This has, indeed, proven to be a key to the understanding of the electrolyte problems of tissue.

Measurement of Tissue Compartments in the Body as a Whole. Since chloride is present in certain cells such as those of the blood, kidney, and stomach, chloride analyses of the whole body indicate a value which is somewhat larger than the true extracellular space. Nevertheless, as a first approximation useful information concerning changes in extracellular volume can be had from the total chloride of the body or from measurements of the volume of distribution of bromide, which appears to be a valid

measure of the total chloride (16). A variety of other materials have been suggested for measuring the extracellular fluid in man. Of these perhaps inulin (17) most nearly estimates the actual extracellular volume.

The fat content of the body may be assessed from the specific gravity (18).[3] The total water can be measured by the distribution of deuterium oxide or antipyrine (19).

Thus means are at hand for measuring in man the major compartments of the body and the concentration of intracellular water. Only fragmentary data are available to date on these values during ageing.

PHYSIOLOGICAL SIGNIFICANCE OF HISTOCHEMICAL CHANGES IN TISSUE

Edema and dehydration

Knowledge of the proportion of extra- and intracellular phases of a tissue, and the changes which may have occurred in the concentrations of constituents of one or the other, provides information of physiological importance.

For example, the problems of edema and dehydration, which assume so much importance during ageing, are directly interpretable in terms of what has happened to the two phases of a tissue. If there has been a marked increase in the fluid of the extracellular phase, one clearly recognizes the existence of clinical edema. However, a less noticeable fluid increase may have taken place which, though escaping clinical detection, is none the less real. Such "occult edema", which is often surprisingly extensive, may be estimated quantitatively by the histochemical procedures previously outlined. Another possible change is an increase in the water concentration of the intracellular phase. This would be described as an intracellular edema, but its clinical detection would be difficult. Darrow and Yannet (20) discussed the possibility of shifts of water into the cells or into the tissue spaces, and were able to conclude that they had produced an intracellular edema as a result of the intraperitoneal injection of glucose solutions. Expèriments carried out by Eichelberger and Hastings (21) have shown that both intra- and extracellular types of edema may be experimentally realized and their amounts measured.

The converse condition of dehydration of tissue may also be studied in a similar manner. Here one may encounter a decrease in either the extracellular phase or the intracellular phase or both. From simple water determinations on a tissue, no interpretation of the nature of the change which has occurred is possible. However, by the application of the histo-

[3] According to personal communication a more convenient direct method for measurement of body fat, based on the uptake of a fat soluble gas, is being elaborated by Dr. J. Murray Steele.

chemical approach, it becomes possible to determine which phase has been affected and by how much.

Edema and dehydration have achieved prominence in connection with the problems encountered in the study of senescence. It is only necessary to mention the prevalence of kidney, heart, and blood vessel disorders in later life to justify the investigation of the distribution of water during ageing. The meager results which are so far available on this subject will be discussed in a later section of this chapter.

On the significance of the proportion of extra- and intracellular phases

It is an obvious truism that a metabolizing cell can maintain its normal activity only so long as it can receive materials necessary for its maintenance, and have removed from its interior and immediate environment materials deleterious to activity.

Much attention has been given to the transport of materials to tissues and the removal of waste products from them by the blood. Less attention has been paid to the effect that a change in the proportion of extra- and intracellular phases of a tissue would have on these important problems of transport. It would seem evident, however, that given a certain metabolic requirement, a certain rate of supply by the blood, and a certain rate of transport of materials from the blood stream to the cells, then the volume of extravascular fluid which must be traversed by the material would influence the success with which the metabolic requirement is met. Such an exchange of materials depends not only on rates of diffusion, but rates of movement of extracellular fluid as well. In extreme *extracellular edema*, the nutrition of the cells may be affected by an increase in the distance between the vascular bed and the cells. In *extracellular dehydration*, there may be too little fluid to permit adequate exchange of the end products of metabolism and the normal activity of the intracellular enzymatic reactions may be consequently disturbed.

In other words, it is probable that there is an optimum relation between the mass of extracellular and intracellular phases of a tissue, and deviations from this optimum in either direction may result in a disturbance in the metabolic activity of the cells. Whether or not a departure from this optimum occurs during ageing thus becomes of importance.

The concentration of solids in the extracellular phase

The integrity of the tissue depends on the extracellular solids collagen, elastin, hyaluronic acid etc., which bind the cells together. Changes in these materials might alter the ability of a tissue to withstand trauma. The concentration of connective tissue fibers in the extracellular phase

may also be looked upon as important in connection with the transport of materials to and from cells. If the collagen fibers increase markedly in old age, they may be expected to interfere with the efficiency of exchange of materials between the blood and the intracellular phase. Further quantitative data on this phase of the subject are needed before its importance for the ageing process can be evaluated.

The interpretation of data in terms of the intracellular phase

A further reason for desiring to know the proportion of the phases of a tissue arises from the fact that with such information in hand, one can then express intracellular concentrations and reactions in terms of units of intracellular material, rather than in terms of the tissue as a whole.

For example, it sometimes transpires that the metabolic activity of a tissue, such as the thyroid gland, is found to be normal if expressed in terms of its intracellular phase, whereas it would appear to be abnormally high if it were expressed on the basis of its total mass.

Furthermore, it is conceivable that it will be highly important for the understanding of the ageing process to know of the changes in actual cell composition which occur with time. The concentrations of enzymes and substrates in the cytoplasm are probably of more significance for the function of the organ than the total amounts of these substances present. Similarly, the water content of the cells may be considered of primary functional importance. On this point, some data are available and will be presented subsequently.

Influence of intracellular ionic concentrations on intracellular reactions

The histochemical studies of tissues have provided a means of estimating the intracellular concentrations of certain inorganic constituents, notably potassium and magnesium. To appreciate the importance of knowing the magnesium concentration it is necessary only to recall the long list of enzymes which require magnesium for full activity. A partial list of such enzymes would include hexokinase, myokinase, enolase, various carboxylases, and nearly all phosphatases and phosphate transferring enzymes.

A particularly relevant example is that of the enzyme which transfers phosphate from phosphopyruvate to adenosine diphosphate. This enzyme requires for activity both magnesium (22) and potassium (23) which are primarily intracellular cations. The activity is on the other hand inhibited by both calcium and sodium which are primarily extracellular cations. Potassium has been assigned an important role in the contraction of the actomyosin complex of muscle. Other examples of the specific importance of cations for various enzyme systems are cited by Lehninger (24).

Consequently, on the basis of present information it is probable that a variety of intracellular enzymatic reactions are controlled, in part at least, by the nature and amount of intracellular cations present.

Knowledge of whether the intracellular concentration of ions varies in old age would, therefore, seem to take on added interest, because of the light such knowledge would shed on the changing metabolic reactions in ageing.

In the foregoing sections, we have been concerned largely with the rationale and methodology of histochemical studies; we have emphasized what can be learned, rather than what has been learned, by such a method of attack. In the remainder of this chapter, we have collected data capable of histochemical interpretation which is pertinent to the problem of ageing These data have been grouped into two divisions: 1) those concerned with ageing during growth, and 2) those concerned with ageing after growth has ceased.

Changes with Age

There have been relatively few investigations of ageing carried out with a view to making the type of histochemical interpretation of the data just outlined. There are, however, accurate data originally obtained for other reasons, from which it is possible to draw tentative conclusions concerning the nature of some of the histochemical changes during growth and senescence. It has been possible also to combine the results of various investigations when a single investigation has not furnished the requisite information.

It would be difficult to discuss ageing without mentioning the changes to be found in the water content of tissues. That senescence is associated with a progressive dehydration is an idea that has been long and widely held, although quantitative evidence to be presented subsequently does not appear to support this concept.

It is natural that the idea of dehydration with age should have arisen because of the obvious appearance of shrivelling and desiccation of the aged. Furthermore, if one actually determines the water content of tissues during *growth*, there is observed a progressive dehydration of nearly all organs, and one is tempted to extrapolate these striking data into old age. The changes taking place during growth are often spoken of as "ageing" processes without a sharp differentiation being made between the changes leading to a vigorous adult state, and the alterations which are correlated with a decline of vigor in old age. There seems, however, to be no *a priori* reason for believing that growth and senescence are necessarily part of the same process except, perhaps, that from species to species the lengths of these two phases of life are usually of the same order of magnitude. Para-

doxically, senescence bears, in some respects, a superficial resemblance to childhood. Should one, therefore, expect the chemical changes initiated during growth to progress further in the same direction in old age, or might one expect them equally logically to reverse their direction?

To reach a definite answer to this question with the limited data available is, perhaps, not possible today; but the fact that such a question exists justifies the examination of the evidence for the nature of the changes during growth on the one hand, and senescence on the other.

Growth

Total Organism. The growth of the animal as a whole from the earliest embryonic stage to *maturity* is characterized by a progressive decrease in water content. On this point, there is excellent agreement. Casually inspected, the data suggest profound changes in the composition of cells during growth.

For example, in table 1 are shown the data of Murray (25) on the chick embryo from the sixth to the eighteenth day of incubation. The fat-free, feather-free, bone-free dry weight rises from 47.8 grams per kilogram on the sixth day to 103.6 grams per kilogram on the eighteenth, that is, a gain of 217 per cent. During the same period, the chloride content falls from 82.1 to 63.4 milliequivalents per kilogram of water. Of the changes in chloride during embryonic development, Needham (26) said: "It is difficult to know what significance to attach to this diminishing concentration."

It seems possible, however, to give a morphological interpretation to these data in the light of modern histochemical concepts. Murray gives figures for the loss of water from the egg during incubation. If it is assumed that the extracellular chloride concentration on the sixth day is 100 milliequivalents per kilogram of water and increases inversely with the change in total egg water, one may calculate the proportions of cells in the developing embryo, and the average water content of these cells. As a result of such a calculation, the concentration of total cell solids would appear to be 231 grams per kilogram of cells on the sixth day and 246 grams per kilogram on the eighteenth day, a negligible change in intracellular solids. There is no particular trend with age. This is in sharp contrast to the impression one might have obtained from the original data—namely, that the cell solid contents had increased greatly during growth. If the above interpretation is correct, the proportion of cells in the tissue rises from 171 grams of cells per kilogram of "net total tissue" (i.e., bone-free, fat-free, feather-free) on the sixth day of incubation, to 396 grams per kilogram on the eighteenth day, with a corresponding decrease in extracellular fluid. That is, the increase in total solids in the tissue is largely due to a relative increase in cells, rather than to changes in the cells them-

selves. On the basis of these data and other data of the same type which lead to the same conclusion, it is tempting to postulate that *a given cell type regardless of age has a composition restricted within narrow limits.*

The concept of increasing concentration of cells per unit of tissue during growth is an exceedingly old one, but has received surprisingly little modern popularity or exploitation. However, as early as 1855, Schlossberger recognized the importance of this concept (27). Preyer (28) considered that the high water content of embryonic tissues might be due to a physiological infiltration with lymph. Needham (26) mentioned "the possibility that the decreasing water content of embryos may be simply an index of the decreasing amount of primitive connective tissue ... and its contained lymph." Shohl (29) and Stearns (30) concluded that the relative decrease in both chloride and sodium during human development was the consequence of a fall in the proportion of extracellular fluid. But the majority of discussions concerning the chemistry of growth clearly imply that the protoplasm itself becomes progressively desiccated.

TABLE 1

Effect of growth on the composition of the embryo of the chick

(Murray)

Except as noted, values are corrected for fat, feathers, and bone*

Age	Weight (uncorr.)	Solids (uncorr.)	Solids (corr.)	Cl	Extracell † (Cl)	Extracell phase	Cell phase	Cell‡ solids	Cell solids
	gm.	gm./kg	gm./kg	mEq./kg H_2O	mEq./kg H_2O	gm./kg	gm./kg	gm./kg tissue	gm./kg cells
6	0.423	56.1	47.8	82.1	100	829	171	39 6	231
7	0 735	58.5	49.5	81 5	101	815	185	41.4	224
8	1.089	62.6	52.8	79.3	101	793	207	45.0	217
9	1.879	69.9	59.5	80 4	102	796	204	51.6	253
10	2.661	68.4	56.7	76.7	102	759	241	49.2	204
11	3.75		[62]	74 8	103	730	270	[55]	[203]
12	5.10	84.7	69.0	70 5	103	692	308	62 1	202
13	6.84	102.0	82.1	68 6	104	666	334	75 5	226
14	8.97	122.5	97.1	68 8	101	670	330	90.5	274
15	11.46	152.8	103.7	67.4	104	654	346	97.2	281
16	14 39	161.0	95.9	66 2	104	642	358	89.3	249
17	17.95	172.2	100.9	63.4	105	610	390	94.9	243
18	22.03	176 4	103.6	63 4	106	604	396	97 6	246

* The bone was estimated as equal to the solids of the ash in excess of 9 grams per kilogram of tissue.

† [Cl] assumed equal to 100 mEq./kg extracellular water at 6 days and assumed to increase inversely with the total water of the egg contents.

‡ 1 per cent of the extracellular weight is subtracted from "Solids (corr.)" to correct for extracellular salts

Human data. The development of the human fetus resembles that of the chick in many respects. There is a similar relative increase in dry weight and fall in chloride. This is illustrated by the data of Iob and Swanson (31) for the composition of seventeen human fetuses ranging from 2.5 to 10 lunar months in age.

The values of substances pertinent to the present discussion are given in table 2. The results have been converted to a fat-free, bone-free basis.

TABLE 2

Variation during human fetal development in phase relations and cell water contents

(Iob and Swanson)

Age, lunar months	Weight	Fat-free* solids	Bone*‡	Cl†	K†	Cell† phase	Cell†§ solids	Cell solids	K
	gm	*gm/kg*	*gm/kg*	*mEq/kg*	*mEq/kg*	*gm/kg*	*gm/kg*	*gm/kg cells*	*mEq/kg cells*
3.2	23 9	60	4 0	21 2	8.2	716	54	75	11
3.7	59 4	70	4 4	56.9	28 0	505	61	121	55
4.3	114 5	107	7 7	78.1	43.3	320	93	290	135
5 1	259	120	12 0	77 5	43.8	325	102	307	135
5 4	335	117	11 5	75.3	36 1	334	100	299	111
5.7	490	118	16 6	70 7	37 7	385	97	252	98
6 2	590	135	16.4	72.0	40 7	374	114	305	109
6.4	570	134	14 1	74 2	31 3	354	115	325	88
7 2	1010	126	12 3	64 2	39 8	442	109	247	90
7 6	960	150	17.8	64.2	38.6	442	128	289	87
7 7	1205	145	14 3	71.2	49 1	380	127	335	129
8.2	1555	164	15 5	68 6	46 0	403	145	359	114
8 2	1545	149	14 8	67.7	45 7	412	130	316	111
8.4	1615	157	15.3	66 8	47.1	419	138	329	112
10.0	2915	191	22.4	56 1	47 2	512	168	326	92

* Calculated on the basis of total fat-free tissue.
† Calculated on the basis of fat-free, bone-free tissue.
‡ Bone calculated from calcium by formula. Bone (gm) = 0.102 (mM Ca − 5)
§ Corrected for bone and for extracellular salts = 1 per cent of extracellular fluid.

The bone was estimated from calcium values on the assumption that each mol of calcium represented 102 grams of bone. This would seem to be legitimate since one mol of calcium is the equivalent of 100 grams of calcium carbonate or 103 grams of calcium phosphate; thus, variations in the ratio of carbonate to phosphate in the bone would have almost no effect on the calculation. A correction of 5 millimols per kilogram was made for calcium in solution in the tissue. It is gratifying that bone estimates based on ash weights (see below) in this series agreed with those based on calcium, with a standard deviation of only 2.6 grams per kilogram. The mass of the extracellular phase was calculated from the chloride figures by using an

assumed value for extracellular chloride of 115 milliequivalents per kilogram. The use of this normal adult figure for extracellular chloride does not appear unreasonable since the data summarized by Needham (26) suggest that maternal and fetal serum have approximately the same chloride content.

In general, the development is characterized by a progressive fall in chloride and a rise in potassium, bone, and "net" solids. It is of extreme interest that the youngest two specimens show very low chloride values. The high potassium values at 4.3 and 5.1 months are likewise exceptional and might tend to obscure the otherwise steady upward trend of potassium.

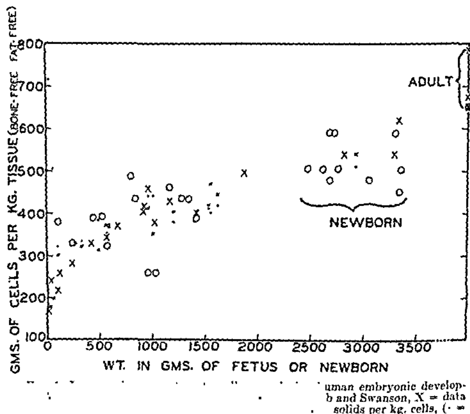
These changes in constituents have been interpreted to signify that from the 4th to the 10th fetal months there is a progressive rise in the proportion of cells. From a value of 320 grams per kilogram at 4.3 months, the cell mass increases to 512 grams per kilogram at term. The 3.2 and 3.7 month fetuses show strikingly high cell proportions, and further studies of this very early period would be of great interest. The concentration of solids, and of potassium in the cells fails to show any consistent trend with age, except in the two youngest specimens already mentioned.

The results of other investigators are in essential agreement with the findings of Iob and Swanson. Since chloride and dry weight values have not always been determined in the same specimens, a graphical representation of the data is given, designed to demonstrate the compatability between the changes in chloride and cell solids (Fig. 1). The fetal weight is plotted against the proportion of cells in the bone-free, fat-free fetus. The data used were taken from Aron (32) who summarized the results of various authors. The values calculated from the data of Iob and Swanson are included for comparison.

The proportions of cells were calculated in two different ways: First, from chloride data, following the procedure outlined above; second, from the cell-solids which were assumed to be present in the cells at a constant level, arbitrarily chosen as 310 grams per kilogram. The total solid figures were converted to cell solids by correcting for fat, bone, and extracellular solids. The bone correction was made on the assumption that the bone salts corresponded to the ash weight less 10 grams per kilogram for salts in solution in the tissue. The extracellular salts were calculated from a rough preliminary estimate of the extracellular fluid, one per cent of which was considered to be salt. Both methods of calculation of the cell mass agree satisfactorily, and suggest that at a fetal weight of 250 grams, there are only about 325 grams of cells per kilogram of "net" tissue. At term, the proportion of cells has apparently risen to 480–550 grams per kilogram and continues to rise thereafter to the adult level of approximately 700 grams of cells per kilogram of bone-free, fat-free tissue. The agreement

between the two methods of calculation during growth of the human organism from a weight of 250 grams to that of 60 kilograms constitutes support for the thesis that cells vary in their abundance during growth without much change in water content.

INDIVIDUAL TISSUES. The study of the growth of individual tissues may be expected to yield more consistent results than might be anticipated from



uman embryonic develop-
b and Swanson, X = data
solids per kg. cells, (· =

observations on the whole animals, since during development, one type of cell may grow more rapidly than another. This might lead to a shift, for example, in the average cell-water content.

In at least three species, rat, cat, and chicken, *skeletal muscle* growth follows the same general pattern of decreasing concentration of water and chloride accompanied by increasing total concentrations of cellular constituents. Interpreted histochemically the data signify a decreasing proportion of extracellular fluid with lesser changes within the fibers.

The recalculated data of Hines and Knowlton (33) manifest a remarkable

stability of fiber water concentration from 15 to 336 days of age (table 3). The observed fall in total water concentration is thus explained completely by a decrease of extracellular fluid to a third of the initial value. Similar if less consistent data have been calculated from values of Barlow, Slinger,

TABLE 3

Effect of growth on rat skeletal muscle

(Hines and Knowlton—recalculated)

Data on fat-free basis

Age in days	15	30	60	90	120	180	336
Number of animals	20	23	22	16	15	13	13
Observed data							
Water—gm./kg. tissue	816	795	776	764	763	763	765
Chloride—mEq./kg. tissue	32	21	16	13	14	13	14
Derived data							
Muscle fibers—gm./kg. tissue	688	818	861	883	879	885	885
Water—gm./kg. fibers	733	749	740	733	731	731	731

TABLE 4

Effect of growth on chicken breast muscle

(Barlow, Slinger, and Manery—recalculated)

Data not fat-free

Age in days	3	7	28	124	270–427	566–1825
Number of animals	10	10	10	10	8	5
Observed data						
Water—gm./kg. tissue	835	826	772	731	734	735
Chloride—mEq./kg. tissue	53	32	19	18	12	9
Derived data						
Muscle fibers—gm./kg. tissue	600	767	867	884	926	944
Water—gm./kg. fibers	735	778	739	696	713	719

and Manery (34) for the white leghorn (table 4). Extracellular fluid fell from 400 gm. to less than 100 gm. per kilo of muscle *during growth, without* consistent change in hydration of the fibers. Likewise during growth in the cat, Yannet and Darrow (20) found that the extracellular fluid, as measured by either sodium or chloride, fell by half without significant change in the intracellular concentration of water, potassium, phosphorus, or nitrogen (table 5). Yannet and Darrow point out that histologically there

has occurred an increase in the size of the individual fibers with a relative decrease in the size of the interstitial spaces. The histological and histochemical data appear to complement each other and suggest that the muscle fibers grow by the formation of additional cytoplasm similar in composition

TABLE 5

Effect of growth on muscle, liver, and brain of cats

(Yannet and Darrow)

A = cats weighing 300-800 gm. (approximately 1-2 months of age)
B = cats weighing 800-2500 gm. (2-6 months of age and older)

Group	Muscle		Liver		Brain	
	A	B	A	B	A	B
	Number of animals					
	11	9	11	9	9	8
Observed data						
Water—gm./kg total tissue	785	770	730	707	846	808
Fat—gm /kg total tissue	20	25	25	60	30	60
Chloride—mEq./kg total tissue	28.2	15.1	31.0	27.7	43.2	39.0
Sodium—mEq /kg total tissue	36.8	23.3	38 6	33.3	55.1	52.5
Potassium—mEq./kg total tissue	80.0	90.4	80.1	73.7	87.0	88.0
Phosphorus—mM/kg total tissue	59.0	66.4	75.6	90.3	76.9	96.3
Nitrogen—gm /kg total tissue	24.7	29.1	23.7	27.4	14.7	16.8
Derived data						
Extracellular fluid—gm./kg total tissue	220	118	244	214	342	301
Cell water—gm./kg cells	746	762	677	681	808	798
Potassium—mEq /kg cell water	139	137	161	145	167	166
Phosphorus—mM/kg. cell water	104	102	155	184	(160)*	(189)*
Nitrogen—gm /kg. cell water	43.6	44.6	47.6	55.7	(29 1)*	(33 1)*

* The presence of an undetermined amount of extracellular nitrogen and phosphorus in brain makes these estimates uncertain

to that already present, and that as the fibers enlarge, they crowd out some of the extracellular phase.

Taking advantage of the conclusion that the muscle fiber water content remains essentially constant during growth, the extensive data of Horvath (35, 36) have been recalculated in histochemical terms (table 6). This reveals a number of features not directly evident from the original data. From 3 to 112 days the proportion of fibers more than doubles. From 12 to 112 days of age there is a steady rise in the fiber concentration of creatine which is about two-thirds phosphorylated at all ages. During the same period, adenosine triphosphate, hexose phosphate and inorganic phosphate

remain almost constant. (The youngest, 3 day old, group is exceptional, all values being higher than at older ages.) The acid-insoluble phosphorus falls with age up to 112 days. This confirms an earlier study of Cole and Koch (37). The bulk of this fraction is phospholipid, and a few actual lipid phosphorus values on young animals (table 13), show the same decrease with age. One is inclined to attribute this decrease to the relative decrease in fiber surface with growth, since some of the phospholipid has been thought to be concentrated at the surface.

In table 7 are shown data from 5 puppy *hearts* contrasted with those of 16 adult dog hearts (Hastings, Blumgart, Lowry and Gilligan (38)). Although the puppy myocardium shows a higher water-content than the adult tissue (803 grams per kilogram as compared to 786), the muscle fibers themselves appear to have the same water-content in the young and in the adult (736 as compared to 734 grams of water per kilogram of fiber). Although the water-content of the fibers did not appear to change, the proportion of fibers apparently rose from 739 grams per kilogram in the case of young dogs to 789 grams per kilogram in the adult. This is consistent with the changes occurring in the skeletal muscle discussed above. The potassium content of the fibers of the myocardium rose only about 8 per cent during this phase of growth, from 139 milliequivalents per kilogram of fiber water to 150 milliequivalents per kilogram, although the original composite data showed a 17 per cent increase during this interval. This is a further illustration of the difference in the final conclusion whether

TABLE 6

Effect of growth on rat skeletal muscle

(Horvath—recalculated)

Solids and muscle fibers calculated per kilo total tissue; other values mM per kilo muscle fibers.

Age	Number of animals	Solids	Muscle fibers*	Acid insol P	Creatine	Creatine P	ATP P	Hexose P	Inorg. P
days									
3	23	115	389	91	30	18	23	8	12
12	32	201	707	48	20	13	15	6	8
18	19	225	797	41	23	15	15	5	9
23–33	52	227	805	48	30	18	13	8	10
38–48	35	225	797	43	34	21	15	8	9
55–90	37	241	856	34	35	22	14	8	8
112–630	205	246	875	28	37	22	14	6	8
689	16	246	875	28	36	21	14	6	8
768	10	248	881	29	34	22	14	5	8

* Calculated assuming 1 per cent fat and a constant fiber water content of 730 gm. per kg.

the tissue is considered as a whole or whether the phases are treated individually.

Two concordant studies are available of histochemical changes during embyronic growth of the *liver*. That of Dumm (39), with the rat and that of Flexner and Flexner (40–42) with the guinea pig. The picture is complicated by the occurrence of hematopoiesis in the fetal liver and by marked changes in lipid and glycogen consequent to the function of the liver as a storage organ. The distribution status of chloride is ambiguous due to an unknown amount of intracellular chloride in the developing red cells. Flexner and Flexner found that sodium gave much lower extracellular

TABLE 7

Distribution of cells, water, and potassium in the left cardiac ventricle of young and adult dogs

All figures corrected for blood and fat

	5 Young dogs*		16 Adult dogs		Per cent change in ventricle
	Serum	Ventricle	Serum	Ventricle	
Observed data					
Water—gm./kg. tissue	934.5	802 8	925.4	785.9	−2.1
Chloride—mEq./kg tissue	108.8	31.6	110.8	25.4	−20
Potassium—mEq./kg. tissue		75 4		88.2	+17
Derived data					
Cells—gm./kg. tissue		739		798	+8
Extracellular fluid—gm /kg. tissue		261		202	−23
Cell water—gm./kg. cells		736		734	−0.3
Potassium—mEq./kg. cell water		139		150	+8

* Average age = 187 days

fluid values than chloride. Both studies cited reported a remarkable fall in nucleic acid phosphorus during maturation of the liver.

The post-natal data of Yannet and Darrow for the cat (table 6) are easier to interpret. The livers of the older group of cats when compared to the younger group, showed a 12 per cent average decrease in extracellular fluid accompanied by a 17 or 18 per cent increase in the intracellular concentration of both nitrogen and phosphorus, and a 10 per cent decrease in the concentration of potassium in the cells. No significant change is to be seen in the concentration of water in the fat-free liver cells; although before corrections were made for fat, the concentration of water in the tissue as a whole appeared to have fallen from 730 grams per kilogram to 707 grams. These authors suggest that the liver of a young animal can be considered a miniature of an older liver, in

that the liver as it grows merely adds additional cells to itself. They believe that the liver changes reflect an alteration in the metabolic activity or state of nutrition rather than structural changes associated with growth. It has been amply shown by Fenn (43) and others that, when the composition of the adult liver is altered through the deposition of storage materials, there are concomitant changes in water and salts. The observed changes, in the present instance, are in the direction expected had there been a decrease in the proportion of glycogen in the cells of the liver.

The complexity of the *brain* makes its histochemical study both particularly difficult, and particularly necessary. The fetal development of the cerebral cortex of the guinea pig has been examined in a most elegant manner by Flexner and colleagues (40–42, 44). Their methods and results deserve careful study. These workers have used quantitative histological and quantitative histochemical methods as complementary tools. Extracellular fluid, calculated from chloride, rises a little at a time when the nerve cells are beginning to spread apart, and then falls almost to half in the adult when the spaces between the cell bodies have become filled with fibers (table 8). Initially, when the nuclei contribute a third of the cerebral mass, the nucleic acid concentration of the cells is very high. As the nuclear mass falls to an eighth of the initial value in the adult, there occurs a parallel but lesser fall in total nucleic acid. It seems probable that desoxypentose nucleic acid undergoes an even more striking decrease. As the cells spread out, and their processes develop, the concentration of phospholipid rises, and there develops an excess of sodium over that calculated in the extracellular fluid. Although the authors assign this extra sodium to the cellular phase, it is possible that it is instead associated with phospholipid anion of myelin sheaths. Judging from the analysis of peripheral myelinated nerves, the aqueous portion of myelin would appear to contain electrolytes of a nature and concentration resembling more closely the salts of the extracellular fluid than those of the cells (Tupikova and Gerard, (45)). In view of the changing form of the nerve cells, the calculated water concentration is remarkably constant. The protein content is also nearly constant during embryonic development but rises a little in the adult.

Yannet and Darrow found changes in the growing cat brain (table 6) which concur with the guinea pig data, except that all the sodium could be accounted for in the extracellular fluid. Compared to those of the younger group, the older cat brains contained 12 per cent less extracellular fluid per kilogram, and the concentration of potassium in the cell water of the brain remained constant during growth. Likewise, calculations indicate that the water content of the brain cells remained essentially the same in the young and old cats.

In general, histochemical studies of the growth of individual tissues are in accord with investigations of the development of the entire organism, and furnish little evidence of progressive changes in the intracellular phase, despite considerable changes in the relative amounts of the tissue phases.

Extracellular fluid changes during growth. It is pertinent to inquire whether during development changes occur in the nature of the extracellular fluid in addition to the changes occurring in its relative amount. Evidence from tissue culture experiments would indicate that cells are what the extracellular fluid makes them (Chapters 3 and 4). One may look to the plasma for signs of changes, since plasma variations will be reflected by alterations in the extracellular fluid. The changes in plasma during growth are fully discussed by McCay (Chapter 7). Some cells, like those of the liver, appear to come in direct contact with the plasma; others, for example the muscle fibers, will only be affected by those plasma changes

TABLE 8

Embryonic growth of the cerebral cortex of the guinea pig

(Flexner and Flexner—recalculated)

	Age—days				
	34–37	39–41	46–51	60-Term.	Adult
Observed data					
Water—gm./kg. total tissue	890	890	885	820	810
Fat—gm /kg. total tissue	10	10	25	55	60
Protein—gm /kg. total tissue	75	70	70	85	100
Tissue phases					
Extracellular fluid—gm /kg. tissue	430	475	470	333	288
Total cells (fat-free)—gm /kg tissue	560	515	505	612	652
Nuclei*—gm /kg tissue	310	210	130	90	40
Cell body cytoplasm*—gm /kg. tissue	150	130	150	170	90
Processes plus glia—gm /kg. tissue	100	175	225	352	522
Cellular constituents					
Water—gm./kg. fat-free cells	830	816	832	801	806
Protein—gm /kg fat-free cells	134	136	139	139	153
High energy P†—mM/kg. cell water	10	10	9	8	8
Other acid-soluble P—mM/kg. cell water	43	46	42	34	28
Sodium—mM/kg. cell water	0	6	24	23	15
Phospholipid P—mM/kg. fat-free cells	32	39	50	69	80
Nucleic acid P—mM/kg. fat-free cells	26	19	14	12	7

* From histological measurements.

† From phosphocreatine, adenosine triphosphate, and adenosine diphosphate.

that would persist in an ultrafiltrate. In this latter category, there are apparently only a few consistent variations so far observed. One of these, the rise in serum chloride during growth in the rat, perhaps reflects a change in acid-base balance justifying further investigation. Another change frequently observed during growth is an increase in the serum protein level. It is conceivable that the low serum protein contents in the young contribute to the abundance of extracellular fluid in the immature tissues.

Summary

To summarize the histochemical changes during growth, it may be said tentatively that evidence from a variety of sources suggests the association of *growth* in tissues with a relative increase in the proportion of cells, and a resultant decrease in the amount of extracellular fluid, with little sign, thus far, of marked alteration in the composition of the intracellular or extracellular phases. These conclusions are at variance with the view that cells undergo a progressive dehydration during development. Certain changes with growth in the composition of the cells must be recognized, which largely reflect changing proportions of the intracellular subunits. Thus, in liver and brain as the nuclear-cytoplasmic ratio decreases the cell concentration of nucleic acid falls. It would, indeed, be surprising if numerous changes, both chemical and functional, are not recognized as the growth process is studied more closely. The similarities in composition between young and mature cells cannot be taken to indicate that differences do not exist, since the concentrations of only a few simple substances have been used so far as criteria of change. It is, however, pertinent to point out that the relative constancy of these few cell components was at first obscured in the original data by the changing proportions of intra- and extracellular phases.

It would seem of practical advantage to make increasing use of histochemistry in growth studies to distinguish real changes in cell composition from apparent variations due to changing proportions of cells. By this means it should be possible to obtain a more intimate picture of the quantitative developments which take place in the growing organism.

Senescence

When one considers the changes taking place during the period between maturity and old age, one finds unfortunately that data suitable for histochemical treatment are rather scarce.

Berger et al. (46) have measured the total body water, with antipyrine, and the bromide space in men and women of different ages. Although they believe that the true extracellular space is only about two-thirds of the bromide space, their data would seem to provide a valid measure of

changes in intracellular and extracellular water (table 9). The total water concentration of the body is not consistently changed with age, but there is a steady shift in this water from the cells to the extracellular spaces, or at least to the bromide space. Assuming that the true extracellular space is two-thirds of the bromide space, this would represent the replacement of about a quarter of the cells of the body by tissue fluid.

In the interpretation of these changes, it may be instructive to consider the data of Keys and co-workers on the effect of inanition on extracellular and intracellular volumes (47). A group of about 20 young men fasted for 24 days during which time they lost 23 per cent of their original weight.

TABLE 9

Effect of age on cellular and extracellular fluid in man

(Berger et al.—recalculated)

Age group	No of persons	Mean wt	Total H_2O	Bromide space	Intracellular fluid
Males					
		kg	ml/kg.	ml/kg.	ml/kg.
20–39	12	70.3	519	253	266
40–59	22	62.6	534	281	253
60–79	14	59.1	500	278	222
80+	3	48.6	538	344	194
Females					
20–39	18	64 9	431	239	192
40–59	4	60.8	434	251	183
60–79	5	60.7	413	261	152
80+	4	43.4	488	352	136

Extracellular fluid was estimated from the thiocyanate space. The fat was measured from the body specific gravity. It will be seen that about 40 per cent of the weight loss was fat, and the rest of the loss was chiefly from tissue cells (table 10). The absolute amount of extracellular fluid actually increased and the relative increase was quite large. There was no decrease in the amount of circulating plasma protein to explain this "edema". It would seem that both inanition and ageing result in a relative increase in extracellular fluid. Apparently, when there occurs a shrinkage or loss of cells the extracellular spaces do not contract.

Simms and Stolman (48) have obtained human material from autopsies after accidental or homicidal deaths in otherwise apparently healthy persons. Comparison was made between a younger group of 11 individuals ranging in age from 30 to 40 years, and an older group of 6 persons all

over 70 years, averaging 75 years of age. In table 11 are shown the average percentage changes between the older and younger groups for sodium, potassium, calcium, magnesium, chloride, phosphorus, nitrogen, water,

TABLE 10

Effect of starvation on body compartments

(Keys et al)

	Bone*	Red cells	Plasma	Fat	Extra-cellular† fluid	Tissue cells
Control period—gm./kg. body wt	40	39	45	139	190	574
24 days fasting—gm./kg. body wt.	53	50	65	52	275	555
gm./kg. original wt.	40	29	50	40	212	429
Net change—gm./kg. original wt.	0	−10	+5	−99	+22	−145

* Assumed values.
† Extravascular.

TABLE 11

Differences between tissue water and electrolytes in mature and aged persons expressed as per cent changes observed and calculated from sodium

	Kidney		Liver		Spleen		Psoas Muscle	
	Obs.	Calc	Obs	Calc	Obs	Calc	Obs.	Calc.
Na	+5		+15		+21		+62	
H_2O	+3	+2	+2	+2	+3	+1	+1	+2
Cl	+2	+5	+18	+15	+12	+15	+56	+62
Ca	+60	?	+4	?	+14	?	+33	?
K ..	−19	−7	+6	−6	−13	−6	−7	−11
Mg	−9	−7	+17	−6	−10	−6	−11	−11
P..	−13	−7	0	−6	−8	−6	−12	−11
N.....	−9	−7	+8	−6	−13	−6	−3	−11
Ash ...	−11	−4	+1	−3	−8	−4	−1	−5

The figures represent per cent change between the average of 11 persons 30–40 years old, averaging 35 years, and 6 individuals over 70 years of age, averaging 75 years.

and ash. The first items in the table: sodium, water, chloride, and calcium, in general showed definite increases, whereas the last five items, potassium, magnesium, phosphorus, nitrogen, and ash largely showed decreases. These changes are in the direction that one would expect if there had been an increase in extracellular fluid, since the extracellular compartment contains most of the sodium and chloride and a larger proportion of water than the intracellular compartment, which, in turn, contains most of the

potassium, magnesium, phosphorus, and nitrogen and whose ash weight would be expected to be much greater than that of the extracellular fluid. As a test of the thesis that part, at least, of these observed changes might be explained by a decrease in the proportion of cells with age, a rough calculation was made of the changes that might be expected in the other components if the sodium changes were used as a measure of the presumed increase in the extracellular compartment. Arbitrary normal electrolyte values for each tissue were assumed. The calculated changes are given next to the observed data and the agreement for the changes in the kidney, spleen, and psoas muscle is quite satisfactory. The liver data do not agree with the prediction, and it will be recalled that in the discussion of growth above, a similar failure of the liver to show a constant cell composition was ascribed to the function of the liver as a site for the storage of various foodstuffs. That is, the composition of the liver cells primarily reflects the nutritional state. In this instance, the changes observed with age are not inconsistent with a decrease in liver glycogen and lipid, and a relative increase in extracellular fluid. Such a change would not be surprising in an older individual Changes in the constituents of the heart were small except for potassium and chloride, and were not predicted by changes in sodium. (The data on the heart were not included in the table because experience has shown that analyses of heart tissue, obtained post mortem, are frequently variable and unreliable.) Changes in calcium in the four tissues are in the direction one would expect from increases in the extracellular phase; but it does not seem possible, at present, to state what portion of this calcium is intra- or extracellular. In the case of the kidney, of course, the possibility of metastatic calcification must be borne in mind. The 6 to 10 per cent changes in the proportion of intracellular phase required to explain the above data would probably escape detection by any but the most elaborate histological examination.

It must be mentioned that Simms and Stolman observed that the presence of extensive disease processes in younger individuals produced changes in tissues not directly concerned in the primary disorders. The changes were less extensive, but of the same nature, as those found in older persons. This raises the disturbing question of the extent to which chronic disorders have contributed to the changes found in the aged. It is generally agreed that older individuals are rarely free from demonstrable pathological changes. One must unfortunately consider the possibility that some of the chemical changes found in senescence are only indirectly due to age itself.

Confirmation of these findings of Simms and Stolman may be found in data from tissues of rats analyzed at 60, 603, and 988 days of age. Ten days in the life of a rat may be considered as the equivalent of perhaps a

year in the life of man. Data for intermediate ages are available in the original publications (49, 50). We are primarily concerned here with comparison between the latter two groups which represent middle age and extreme old age. It may be noted, however, that the skeletal muscle of the 60 day groups shows some of the characteristics of immaturity described above, viz. a slightly larger proportion of extracellular fluid, and an elevated concentration of phospholipid in the muscle fibers.

Extreme age results in the *skeletal muscle* in an increase in water, sodium, and chloride and a decrease in acid-soluble phosphorus and potassium (table 12). Interpreted histochemically, age has resulted in a near doubling of the extracellular fluid without change in water or potassium concentration in the cell (table 13). The moderate increase in lipid concentration is of interest, since like the change in extracellular fluid, the change with old age is the reverse of the change with growth. There is a suggestion that the extracellular compartment contains a lower proportion of solids in old age. In general, then, in ageing as in growth, the muscle of the rat undergoes definite alterations in the proportions of its phases, but the composition of the intracellular phase changes comparatively little.

Atrophy is commonly considered an attribute of many old tissues. The muscle, for example, in a very old individual is greatly reduced in mass in comparison to its bulk at the height of vigor. It is not entirely clear how much of this decrease in total mass has been due to actual loss of fibers and how much is to be accounted for by a decrease in their average size. The extensive measurements of Bucciante and Luria (51) demonstrate the occurrence of hypertrophy in the surviving fibers of the ocular muscles in the 8th and 9th decades, but their studies were purposely made on the eye muscles in which activity is not greatly restricted in old age. It is reasonable to believe that the fibers of larger leg muscles, for instance, undergo considerable atrophy of disuse in later life.

It is, therefore, fitting to compare senile changes with experimental atrophy. One might predict that a decrease in size of muscle fibers would reverse somewhat the developments during growth, thereby resulting in a looser tissue with relatively greater amounts of extracellular fluid. Hines and Knowlton (52) produced atrophy in the rat gastrocnemius muscle by three different procedures: denervation, tenotomy, and starvation (table 14). Marked changes were observed, varying with the duration of the experiment. Twenty-eight days after denervation, the muscle had lost 72 per cent of its mass. During this time there occurred a 275 per cent rise in chloride content, and a 2 per cent increase in water content. The potassium level fell 25 per cent accompanied by a 40 per cent decrease in acid-soluble phosphorus per unit weight of tissue. Hines and Knowlton interpreted these changes as signifying that, as the muscle fibers underwent

marked atrophy, there occurred only a slight decrease in the absolute amount of extracellular tissue. Thus, there would be a large *relative increase*

TABLE 12

Changes in rat tissues with age—original data

60 day group comprised of 6 rats, av. wt. 111 gm.; 603 day group comprised of 47 rats, av. wt 308 gm.; 988 day group comprised of 7 animals, av. wt. 244 gm. All data on blood-free basis, all but brain and kidney on fat-free basis.

Age	H_2O	Fat	Collagen plus elastin	Cl	Acid-soluble P	Lipid P	Residual P	Na	K	Ca	Mg
					Skeletal muscle						
days	*gm*	*gm.*	*gm.*	*mEq*	*mM*	*mM*	*mM*	*mEq.*	*mEq.*	*mEq.*	*mEq*
60	779	*	12	16	61	13	5.4		118		
603	761		13	13	60	9	5.6	21	110	3 2	25
988	790		14	23	50	11	5.6	32	99	2 6	25
					Heart						
603	780	32	10	25	37	23	12	40	80	2.2	18
988	785	30	12	26	37	26	11	41	73	2.0	18
					Liver						
60	750	43	3	32	46	40	30				
603	759	49	3	30	46	35	31	27	102	2.3	20
988	756	42	2	27	43	36	33	26	103	2.1	21
					Brain						
603	773	96	†	35	33	56	16	46	99	4.0	13
988	770	87		34	32	51	16	51	94	3.3	12
					Renal cortex						
60	738	44	7	46	40	37	26		72		
603	779	40	11	54	32	27	22	76	63	4.8	
988	783	32	17	59	29	24	21	88	54	3.1	

* Variable and not believed to be relevant.

† Averaged 6 gm. with other animals.

in the extracellular phase. These authors found that the cell water contents appeared to remain constant, if it were assumed that the extracellular compartment contained 20 per cent solids, an assumption that might be checked by collagen determinations. It is of interest that potassium and

TABLE 13

Histochemical changes in rat tissues—derived data

See table 10 for composition of groups. E and C are calculated per kilo blood free, fat-free tissue, except for brain and kidney which are blood-free only. H_2O is calculated per kilo of cells, $(Co + El)_E$ is collagen plus elastin per kilo of E, all other data per kilo of cell water.

Age	E	C	$(Co + El)_E$	$(H_2O)_c$	$[ASP]_c$	$[LP]_c$	$[RP]_c$	$[Cl]_c$	$[Na]_c$	$[K]_c$	$[Ca]_c$	$[Mg]_c$
					Skeletal muscle							
days	*gm.*	*gm*	*gm.*	*gm*	*mM*	*mM*	*mM*	*mEq.*	*mEq*	*mEq*	*mEq*	*mEq.*
60	150	850	87	756	95	20	8.4	*		182		
603	126	874	108	742	93	14	8.6		7	169	4	38
988	222	778	73	752	85	18	9.6		4	169	2	42
					Heart							
603	249	751	39	734	67	41	21	*	11	143	2	32
988	272	728	41	739	68	47	20		9	133	2	33
					Liver							
60	219	781	14	704	82	73	55	†				
603	197	803	15	724	80	61	53			175	2	33
988	211	789	10	715	76	64	60			178	2	31
					Brain							
603	310	594		790	69	120	35	*	5	209	7	28
988	315	598		772	67	116	36		16	198	5	26
					Renal cortex							
60	280‡	720	21	§	83	78	56	32		153		
603	413	587	26		82	69	57	19	47	160	10	
988	441	559	37		76	67	57	25	66	145	4	

* Assumed to be zero.
† Assumed 13 mEq. per kilo cell water.
‡ Extracellular tissue plus urine.
§ Assumed to be 650 gm. per kilo of cells (not fat-free).

acid-soluble phosphorus showed much less variation when calculated on the basis of cell-water than when based on the total tissue weight, thereby suggesting that potassium, acid-soluble phosphorus, and intracellular solids escape during atrophy in proportion to their concentration in the cells.

Thus, the atrophy of muscle produces histochemical changes which re-

semble, as far as data permit comparison, the alterations observed in old age. The atrophic changes may be supposed to consist in a proportionate loss of individual cytoplasmic elements from the intracellular compartment accompanied by an increasing prominence of the extracellular components.

The data of tables 12 and 13 indicate for the rat *heart*, *liver* and *brain* remarkably little change in extreme age in either amount or composition of the extracellular or intracellular phases. Nevertheless, in the heart there is found a slight increase in the extracellular phase, and the cell concentration of lipid phosphorus increases as was found for skeletal muscle. Both heart and brain show a minor fall in the intracellular potassium concentration which in the brain is replaced by sodium.

TABLE 14

Changes induced by atrophy in the gastrocnemious muscle of the rat

(Hines and Knowlton)

	Weight lost by muscle	Water content	Extra-cell water	Cell* water	K	Acid-sol P	$[K]_c$	Acid-sol P
		gm/kg. tissue	*gm/kg tissue*	*gm/kg. cells*	*mEq/kg tissue*	*mM/kg tissue*	*mEq/kg cell H_2O*	*mM/kg cell H_2O*
Normal		758	108	751	94	51	145	78
Denervated 3 days	6.7	765	138	758	91		146	
Denervated 7 days	28.2	762	158	752	79	60	131	82
Denervated 14 days	49.9	768	212	756	78	42	140	75
Denervated 28 days	72.3	772	298	756	72	31	151	
Tenotomy 10 days	27 9	770	159	762				
Fasting 8 days	26	771	146	764				
Fasting and denervation		773	198	765				

* Assuming extracellular phase originally contained 20 per cent solids.

The rat brain may resist age more successfully than human. Although histochemical data are not at hand for human material, Strobel (53) has reported data indicating that the human brain can be added to the list of tissues in which a decrease in total solids occurs in old age. Strobel's values for the dry weights of cortex, medulla, brain stem, and cerebellum are given at various ages (table 15). There was found to be a 100 per cent *increase in dry weight between birth and maturity in all four parts of the* brain. This was followed in senescence by a consistent decline in total solids ranging from 8 to 15 per cent. It is to be hoped that the appearance of additional data will permit the interpretation of these changes in the brain. At present, it is only possible to speculate that the loss of cells from the ageing brain might leave space for greater amounts of extracellular fluid with its high water content.

The changes in the rat kidney (tables 12 and 13) are more pronounced

than in any of the other rat tissues examined Furthermore these changes are present to a considerable degree in the middle aged group. Other data at intermediate ages indicate that the kidneys of the 60 day group have a mature composition, and this group therefore provides a suitable control The data suggest that in the oldest group there has occurred a 25 per cent decrease in the proportionate cell mass without much change in cell composition, except that there appears to have been exchange of sodium for some of the cellular potassium However, without data on functional fluctuations in sodium and potassium, this change ought not to be emphasized. The changes in the rat kidney are strikingly similar to those observed by Simms and Stolman for man, which have been cited above.

The present interpretation of the water increases in senescence and atrophy may or may not be correct; nevertheless the hydration itself appears to be a rather constant finding. In view, however, of the deep-

TABLE 15

Effect of senility on the dry-weights of various parts of the human brain

(Strobel)

Dry-weight—gm. per kilogram of tissue

	No of persons	Cortex	Medulla	Brain stem	Cerebellum
Newborn	2	89.5	91.5	111.2	108.0
Adult (average age = 30 years)	4	153 6	315.8	220 3	201.3
Senile (61–89 years of age)	16	141.7	278.6	190.2	172.1

seated belief that desiccation, and not hydration, is an attribute of the very old, one would desire additional information on water changes in senescence.

Even skin, which has a dried-out appearance in old persons, actually shows a higher water content at 80 than at 60 years of age, according to Bürger and Schlomka (51) (see also Chapter 7).

Summary. In spite of the meagerness of the data, it is perhaps not too early to draw a few inferences concerning the histochemical changes in old age. A change in the water content of many tissues does seem to occur in senescence, but in spite of the widespread belief to the contrary, this change is a hydration, rather than a desiccation. This increase in water may be quite possibly an extracellular edema, and may be consequent to atrophy, the loss of tissue cells, or even to cardiac or renal hypofunc-

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The important question of the extent to which disease processes contribute to the observed chemical changes requires careful consideration

Alterations similar to those found in old age have been observed in the tissues of patients with systemic disorders not primarily affecting the tissues in question. Similarly, muscular atrophy occasions the type of change observed in old muscle—namely, an increase of the extracellular phase at the expense of the intracellular phase.

The situation in regard to the study of senescence is analogous to that in regard to growth. Undoubtedly changes will be found, not only in the proportion of phases, but in the cytoplasm as well. In order to appreciate these changes, it may be necessary to make suitable allowance for changing proportions of cells, blood, fat, collagen, and extracellular fluid. The determination of the histochemical configuration in old tissues may not only permit the detection of intracellular changes, but should give a clearer understanding of the conditions under which tissue enzyme systems function in the aged individual. Such an understanding of the chemical pattern might well constitute a fuller comprehension of the ageing process, and conceivably lead to prophylactic measures which would delay the onset of senescence.

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6

CHEMICAL ASPECTS OF AGEING AND THE EFFECT OF DIET UPON AGEING

CLIVE M. McCAY

Ithaca

"Thou canst help time to furrow me with age, but stop no wrinkle."—Richard II.

"Eine einzige Zahl hat mehr wahren und bleibenden Wert als eine kostbare Bibliothek voll Hypothesen"—Robt. Mayer.

The goal of the biochemist in the study of ageing is to define the process in terms of quantitative chemical changes. The differences between the bodies of a youth and a man of eighty are evident even to the casual observer. These extremes interest the biochemist but his service should be initiated long before the final alterations of the declining years have taken place. He must ultimately detect these changes and define them in terms of quantitative biochemistry nearer the time of their beginning. Here alone lies some hope of reversing reactions which day by day introduce the changes that finally result in senility.

The paucity of biochemical data defining these age changes is due in part to the slow rate at which transformations take place. In no case has a biochemist had the patience to determine such values as the chemical balance of an animal body during a whole life cycle. Perhaps available techniques are still inadequate to detect the continual changes that proceed in the body day by day.

There is no doubt that the life span can be modified considerably by such factors as nutrition and living regime. The biochemist cannot hope to confine his attention to one set of conditions and term this normal state of ageing. It is more probable that he will have to state that certain chemical changes take place in the animal body under certain defined conditions of diet and living. Then he can hope to select those variables that lead to the slowest rates of change in approaching senile degeneration.

In studying age changes the biochemist is first confronted with the problem of experimental animals. Such animals should have relatively short life spans. They need to be large enough to afford analytical samples that will yield accurate values by modern methods. If nutritional variables are to be considered in the hope of retarding human senility the chosen species should consume foodstuffs similar to those of man. The white rat is probably the most useful animal for such biochemical studies today. In addition to this species, chickens and sheep probably afford excellent opportunities in the study of senescence.



FIG. 1. Aged cocker spaniel from the "home for aged, pure bred dogs" at Cornell.

The food of the rat is similar to that of man. The organs of its body are large enough for analyses. Its mean life span is about two years. Large numbers can be maintained at a modest cost. The nutrition is well defined.

Many other species from insects to man have been employed in the past. Some data have been obtained from analyzing the organs and bodies of dogs, swine, rabbits and other domesticated animals. For the most part, however, these species tend to live too long to permit rapid progress in such research. Insects have some advantages for fundamental studies but their nutrition is poorly defined and their bodies are too small for analytical studies upon organs.

Opportunities for the study of ageing by the use of old dogs have been neglected in the past. Throughout the nation are hundreds of pure bred, registered dogs that are kept in kennels for sentimental reasons. The experience of the author indicates that these dogs are gladly surrendered if the dogs are assured of humane treatment. Much nutrition work such as chemical balance studies can be done with no injury to the animals. For some years the kennels at Cornell have made use of such dogs (fig. 1).

Testing of nutritional hypotheses is also possible using man himself for such studies. Much basic information is needed concerning the reflection of given dietary practices upon the ageing process. Our prisons contain many life termers who would gladly engage in such studies. Many of these men would welcome the addition of three eggs daily to their diet and would gladly assume any risk of hardened arteries. Some would be pleased to have a daily allowance of rum or other liquor to determine the effects of the regular usage of alcohol during a period of many years. Long ago the great biochemist, Otto Folin, called attention to our losses in failing to study our prisoners. The escape from boredom would also enlist many in harmless experiments in many homes such as those for veterans.

Growth Rate, Life Span, and Chemical Composition

"These eyes, that see thee now well coloured, shall see thee withered."
—Henry VI

In the middle ages, the monk, Roger Bacon, stated that there were two limits to the length of life of a species. The first of these depended upon the conditions of living such as available foodstuffs and other factors of environment. In the case of man, these variables were thought to be subject to modification and the life span thus subject to extension. However, Bacon believed that the span could not be protracted indefinitely but that every species had a limit set by the Lord, which could not be exceeded. Bacon's concepts seem valid today, because all are aware of the great difference in the life span of animal species. Thus the rat is very old at three years, while an old horse may be nearly thirty.

The possible life span of a given species will probably always remain unknown, however. This fact is of interest to the biochemist in the first place because he can be assured of reasonable success in extending the life span by the control of such variables as those of nutrition. In the second place, he may look for different changes in the body of an experimental animal such as a rat that passes through its life cycle in two years compared to a period twice this long. Thus it was found in the laboratory at Cornell in the case of rats with life spans that had been extended to nearly four years, that the bones were so fragile that they were crushed by the scalpel in the process of dissecting away the muscles (McCay(1)). On the other hand,

rats that died within the period of two to three years, which is usually termed "normal", retained very firm bones that were difficult to crush. Some of the bones of those with the extended life spans were mere shells that floated in water, while the normal bone of a rat that dies at the end of two years always sinks. The end stages were different here although one case may have been the terminal picture of forces acting over a longer period of time. The alternative to consider is a possible modification of the rate and final state as a result of manipulating the nutrition to extend the life span. This may also be an illustration of the tendency of different organs to age at different rates. Thus the bones may seldom degenerate to the point of terminating the life of an animal because some other organ such as the heart tends to break down first.

Growth Rate and Life Span

"Withered, grotesque, immeasurably old."—Wordsworth.

The relation of the rate of growth to the total span of life has been debated since the time of Aristotle. More than a hundred years ago Edmonds (2) devoted a book to the thesis that alternate periods of hardship and prosperity afforded one of the secrets to a long life. He claimed that adversity in youth tended to retard the rate of maturing and estimated that an increase of a year in the duration of infancy tended to increase adult life by seven times this amount.

In early considerations of the effect of growth rate upon total life span, deductions were based upon data from different species. Such relationships were reviewed by Bunge (3), Flourens (4), and Lusk (5). Until modern times little attention has been given to the problem of individual variation within a given species.

However the problem has come to the front due to the recognition that the rate of growth of the whole body is not accompanied by a proportionate rate in the parts of the body. The alteration in the relative size and composition of the parts has a profound influence upon the resistance of the animal to disease, the length of the life span and even the shape of the adult body. The last is well illustrated in the studies of McMeekan and Hammond (6) who have modified the carcasses of sheep and swine by controlling the rate of growth. Hammond has suggested that "in the downward curve of life, it would appear probable that the organs, regions and tissues of the body go into senility in the reverse order from that in which they are developed. It would appear probable that this is because of their different

In the case of cattle, Waters (10), Ashton (11), Brody and others (12) have discussed the effect of different growth rates upon the structure of the body. Jackson (13) has provided reviews of the literature in this field and made many excellent research contributions using the white rat as the experimental animal. In 1937 Jackson observed that the reproductive performance of the retarded male rat exceeded that of the normal.

In spite of the economic importance to animal husbandry of keeping milking animals in production for long periods, little attention has been given to this subject. Rare cows have been kept in production for as long as twenty years but the typical cow is slaughtered when about seven years old. Many breeders of Jerseys and Guernseys feel that the slow growth of these cattle due to the poor food in their native islands led to superior cows. Recently Danish workers have attempted to test this hypothesis using their own breed of Danish Red cattle (14). They divided young heifer calves into three groups. One was underfed, another overfed and a third given an average allowance of feed during the growing period. In calves produced and in "lasting" ability the underfed group proved superior.

Several experimental attempts have been made to determine if slower growing animals have longer life spans. Robertson and Ray (15) kept a group of mice from birth until they died of old age. They determined their rates of growth and total life span. Finally they concluded that those which grew the more rapidly lived the longer. Any such group of animals probably includes diseased individuals. These tend to grow at a slower rate and to die prematurely. Inasmuch as it is impossible to evaluate the extent of disease in such an experimental group, the effect of these members upon the composite growth curve and the total life span cannot be determined. At the same time the conclusions that are drawn from such experiments tend to be dominated by data from this fraction. *For this reason the relationship between growth rate and life span cannot be determined upon a heterogeneous group of animals permitted to grow at the maximum rate of which they are capable.*

Since the time of Robertson other workers have attempted to draw conclusions from groups of rats treated in a similar manner. This matter has been discussed in more detail elsewhere (16). No valid deduction concerning the relationship between the rate of growth and life span can be drawn from such experiments.

For this same reason it is doubtful if this question can be answered in the case of human beings. One cannot attack the problem even if he has growth rates and life span data upon the same group of people.

If the same animal could live twice, it might be forced to grow slowly during one life and rapidly in another. The answer would then be known. Since this is impossible, the nearest approach is to select two groups of

animals at the time of weaning. If these groups are made as nearly equal as possible, they should contain approximately the same number of diseased individuals and this short lived fraction will not dominate the outcome. If one of these groups is obliged to grow slowly and another allowed to grow normally the answer can be obtained.

In the course of studying the effect of retardation of growth in fish due to feeding a low protein diet McCay and others (17) observed that trout retarded in growth outlived those that grew normally. In 1930 experiments were started at Cornell with white rats to determine the effect of retarded growth upon the total span of life. Three experiments of this type have been run. Only an outline of the results will be included here since details will be found in the original reports (18, 19). In all three studies the design of the diets has been similar. In every case these diets have provided every rat with an adequate daily allowance of protein, minerals, vitamins and other essentials so that the retardation of growth was due to an inadequate allowance of calories. This adequacy was tested at various times by permitting the rats to grow when fed the basal plus some source of calories such as sucrose.

The first study with rats was completed in 1934. In this experiment one group was allowed to grow to maturity at a normal rate. Two groups were retarded by reducing the energy of the diet to a level adequate for maintenance but insufficient to permit growth. One group was thus held for more than 700 days and another in excess of 900 days without being allowed to grow to maturity. When they were finally given adequate calories and permitted to grow, they did so although they had already exceeded the mean length of life of this species which is about 600 days. Members of both retarded groups were alive when those that grew to maturity at the normal rate had all died. This indicated that the life span was flexible and that the possibility of its extension was unknown as well as that the retarded animals tended to outlive those that matured normally.

Since this initial experiment conflicted with the common idea that the maximum growth rate of an animal was conducive to the longest and healthiest life, numerous criticisms arose. The most important of these were the following: (a) An accidental selection of animals had placed the long lived ones in the retarded groups. This was very unlikely because the retarded rats had so far outlived the normal animals whose life spans had been recorded previously. (b) An accident and resulting high temperature in the laboratory had wiped out the weaklings leaving a residue of "tough" animals that lived long, among the retarded animals. In a later accident which wiped out a large number of normal rats due to excessive temperature there was no evidence that survivors lived longer than normal. (C) The retarded animals had consumed less protein, minerals and vitamins

and hence less burden had been placed upon the excretory organs such as the kidneys. The second experiment was designed to answer this criticism and to test the thesis that retardation of growth by limitation of calories greatly increased the span of life of the rat.

This second study was planned so that the same amount of protein, minerals and vitamins was fed to each individual, but the animals that were allowed to mature normally were given all the calories they wished in the form of a mixture of sugar and lard. In this second study 106 rats were divided into two groups at the time of weaning. One of these groups contained 33 members. These were allowed to grow to maturity normally. The last one of this group died at the extreme age of 965 days. The accompanying photograph (fig. 2) shows the last two members of this group that lived.

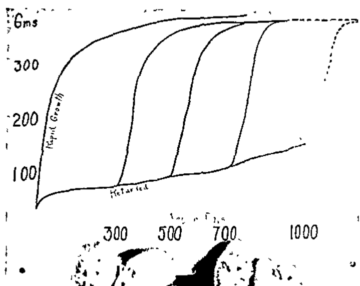


FIG. 2. The last two survivors from the group of 33 rats that were allowed to grow normally in the second retarded growth study. The animal with the tumor was the one that finally lived to be the oldest in this group.

The remainder of the 106 rats numbering 73, were retarded in growth for 300 days. During this period 35 died due to two accidents in losing control of the room temperature, but 38 were still alive at 300 days. These were distributed into four groups, two containing 10 each and two nine each. The first of these groups was fed adequately and thus completed its growth starting at 300 days. The other three were retarded for 500, 700 and 1,000 days. The growth curves are illustrated in the background of figure 2 in which a representative of each group lies in front of its growth curve.

At the time of the death of the last member of the control group, there were still 18 animals alive distributed among the various retarded ones. Only three were alive, however, in the group that matured after 300 days. Even these appeared old in contrast to the group held for 1,000 days (figs. 3 and 4).

The second experiment gave essentially the same results as the first and indicated clearly that the retarded growth was the essential feature. No



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1,000 days of ratardation.

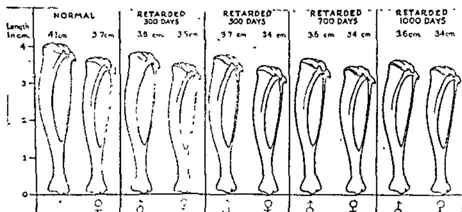


Fig. 4. Diagram to show the ultimate length of the tibia from retarded rats.

evidence was found for any injurious effects of dietary constituents such as high protein levels. This was further confirmed in later studies with protein.

A third retarded growth experiment was now initiated to determine why retardation prolonged the life span. In the two earlier studies, the absence

of tumors during the period of retardation ... Jackson (20) had found a lowered incidence of ear infections in animals retarded for fifteen ... ify the composition of organs so that those ... pathogenic microorganism or else better able ... changes that produce the diseases which ...

The third study was larger and more ... 500 rats were used and facilities were developed ... and humidity relatively constant throughout ... tition of earlier accidents two temperature ... one operating a few degrees above the other.

To determine the incidence of disease in ... animals were killed and studied by Dr. John ... dred days. All teeth were examined by Dr. ... City.

This experiment was designed to answer ... 1) why do retarded animals have longer span ... animals fed an adequate basal diet, does the ... have an effect upon the ageing processes? At ... were placed upon a diet adequate in all ... 200 additional rats were fed the same daily ... all the additional calories they desired. These ... four groups of 50 each. The following additions ... given to one of each of these groups: 1) dried ... 3) dried cooked starch and 4) sucrose.

This final study indicated that rats could ... days and still resume growth in the case of ... for the extension of life span of retarded anim... ment of the chronic diseases that attacked the ... ear (22). Tumors were also slower in develop... partial starvation inhibited the development ... (23) upon mice. Such studies have now been ... reviewed frequently (24).

The type of calories provided with an adequate ... little in regard to the span of life. Sugar, star... equally valuable. However, the males fed the ... quite early due to the marginal level of vitamin ... illustrates the danger of excessive use of a pure ... by human beings since human diets may be ... Diets rich in sucrose tend to inflict hazards up... if these carbohydrates are provided by natural ... or cereals.

The above studies with vitamin E at a marginal level indicate that males can become sterile early in life but the length of the total span is not affected. Retarded males in the above study remained fertile much longer than the controls fed supplements of starch and sugar, although the level of vitamin E was marginal for all. It cannot be determined whether the larger muscle volume of normal rats in contrast to retarded ones, or the carbohydrates increased the need for vitamin E.

Calcification in the tissues of both normal and retarded rats was studied by use of stereo-roentgenographs. Calcification in the hearts increased with age in all rats but proceeded more slowly in retarded ones. Most calcification was found in the auricle. More calcification was found in the kidneys of the control rats than in those of rats retarded in growth.

Calcification of the tubules and spermatic artery of the testes was very common. This reached a maximum among the normal males about 600 days of age while the same high incidence was nearly a year later for retarded rats. The calcification of the aorta was rare in both groups of rats. Some of these data contrast with earlier findings in our retarded growth studies and indicate other variables had entered the study.

In earlier studies, less calcification was found in the hearts of rats kept thin and forced to exercise (22b). Also Hummel and Barnes (25) in the former study of retarded growth found more evidence of calcification in the soft tissues of retarded animals than in those of the controls.

If one were to draw conclusions from these data for guidance of human beings he might summarize by stating: "Eat what you should, after that eat what you will but not too much."

There is a considerable body of literature supporting the thesis that the life span is extended by slower growth. Ingle (26) working with Cladocera effected an increase in life span by retarding the growth rate. In the case of insects, many workers have shown the modifications induced in the various stages of the life cycle by retarding one stage. The studies of Kellogg and Bell (27) with silk worms are typical of insects. Northrup (28) showed a similar effect in the case of drosophila.

Recent reports by Carlson and Hoelzel (29) state that alternate periods of fasting and feeding favored the life span in rats and retarded the development of mammary tumors. Since this did not influence the growth rate of the rats, other favorable influences must result from fasting.

Little attention has been given to the relation between restriction of diet and diseases of bacterial or virus origin. However, Foster and associates (30) have found that mice are less subject to poliomyelitis virus if maintained on restricted food intakes or diets deficient in thiamine.

In general the retarded rat remains active and appears young whatever its age. It is very alert. It tends to go blind in the second and third year

of life. Its pulse rate of 340 beats per minute is about a hundred below the normal. Its erythrocyte count is normal but its blood contains only two-thirds as many leukocytes as the normal rat. Thus in one experiment the mean was 6,400 for retarded rats and 9,900 for normal ones. These findings were consistent in the second and third experiments which were separated by several years and several generations of rats No determinations were made in the first.

These findings in regard to the number of leukocytes and the mean span of life do not accord with those of Reich and Dunning (31) These authors found mean leucocyte counts of 14 to 25 thousand among their strains of rats. They found a correlation between the mean length of life and this count. All of their rats seemed to die relatively young, however, because the highest mean value for length of life was only 650 days while the lowest was less than a year. They failed to describe their diet or environment.

Horst and others (32) found the basal metabolism of retarded rats to be intermediate between younger ones of the same size and larger ones of the same age.

The studies of Lois Will of the basal metabolism of retarded rats indicated that at 850 days of age, heat production per unit of weight was higher than that for the controls but the values were lower per unit of surface area. Retarded rats at 1200 days of age had the same basal metabolism per unit of surface area as rats realimented at 900 or 1150 days of age (33).

Retardation seems to affect the reproductive powers of female animals. Rats seem able to breed at a later date after retardation. In case they are subjected to alternate periods of growth and retardation, the females exhibit normal estrous cycles during growth and abnormal ones during the retarded periods (34).

If both sexes of rats are retarded for long periods and then allowed to grow the male tends to attain a larger size than the female. Both tend to live about the same length of time suggesting that the slower growth rate may be one explanation for the longer life of the female of the species under normal conditions (1).

Nutrition and Life Span

> "*Consequently to preserve life is to use meates and drinks according to the age of the person. For the dyet of youth is not convenient for old age nor contrariwise.*"—Thomas Cogan. The Haven of Health 1596.

Since very early times authors have stressed the importance of diet in preserving the animal body against the encroachments of old age. The past hundred years have produced an embryo science of nutrition. Hundreds of workers give their entire time to advancing this science today. However,

almost all attention has been devoted to the study of the nutritional requirements of growing animals to the neglect of the adult.

The reason for this emphasis upon the growing stage is due in the first place to the ease of studying young animals. The diseases that appear in old age may have started but are unobserved in the young. In the second place, the growing body is a seat of very rapid chemical changes. As a result the effects of different diets become evident very quickly. In the adult, however, body stores have been built within such organs as the liver and the animal is no longer growing—so its needs are less. Therefore, it requires long protracted efforts to produce dietary effects in the mature. Many of the current concepts concerning the nutrition of mature animals are questionable because they are derived from reasoning by analogy, from young, immature animals. Hence the decisions regarding the diets of adults usually represent compromises between food habits established by long usage and modern evidence based upon experiments with developing animals.

Human experience has long shown the value of temperance in the consumption of food. Luigi Cornaro (1464–1566) stressed this in the series of essays written in the late years of his life. Francis Bacon stated, "It seems to be approved by experience, that a spare diet, and almost a pythagorical,—such as is either prescribed by the strict rules of a monastical life, or practiced by hermits, which have necessity and poverty for their rule,—rendereth a man long-lived." Such statements as these comprise the content of many of the works written about diets for the aged. Usually they share the book with some pet theory that the author desires to promote.

In modern times a beginning has been made in relating nutrition to the life span. Osborne and Mendel (35) were fully aware of the problems involved and discussed them in the course of their growth studies. They even made one attempt to keep retarded animals until the end of life, but they lost them prematurely from disease. Slonaker (36) attempted to determine the effect of vegetarian and omnivorous diets upon the length of life of rats. He found the vegetarian rats tended to die much sooner. This early attempt needs to be repeated since advances in the past twenty-five years have probably made it possible to select a vegetarian diet that would give very different results. This early work of Slonaker is of special interest because of the long life of some of his animals.

In a later study, Slonaker (37) studied the life activities of rats fed different levels of meats in the diet. His results, in terms of life span, are summarized in table 1.

These data seem to indicate an optimum of protein near the 14 per cent

level. Due to the methods of preparing the diets, however, it is possible that these differences may have been the result of factors other than the protein. Dried meat was used to vary the protein levels and in each case this replaced varying amounts of a mixture of plant foods The results might have been different if casein had been used to replace starch in the diets.

This study of Slonaker illustrates one useful technique. The animals are paired at the time of weaning to make groups as equal as possible They are then fed a given diet throughout the remainder of their lives. Such factors as reproduction, activity and the development of diseases are then determined. This method is useful if the diet is adequate for all special

TABLE 1

Life span and protein level fed rats

(Slonaker)

Protein level	Males				Females			
	Weight		Age		Weight		Age	
	Mean	PE	Mean	P.E.	Mean	P.E.	Mean	P.E.
per cent	*gm*	*gm.*	*days*	*days*	*gm.*	*gm*	*days*	*days*
10	192	1.8	700	3.7	159	1.0	762	7.2
14	222	1.4	767	5 9	185	1.2	848	7.0
18	191	1.4	760	7.2	198	2.2	810	6.2
22	202	1.7	675	5.7	167	2.2	766	7.4
26	214	1.6	650	3.0	158	1.2	730	7.3

periods, but may give fallacious results if the diet fails to satisfy requirements during the special periods, such as growth, gestation and lactation. Thus a protein level of 10 per cent may prove adequate for an adult not involved in reproduction and fail for a growing animal or it may be sufficient for a normal male and fail for a lactating female. Dietary drains during crucial periods may thus weaken the body of the female and shorten the life span or lead to the development of special diseases.

For the above reasons nutrition students need to employ additional techniques that satisfy the requirements of animals during special periods. Groups of animals that are to remain unbred can be reared to adults with an adequate allowance of protein for growth. During the adult stage protein levels can be compared.

Likewise, studies are needed in which animals are brought to maturity upon different levels of protein and then maintained under the same conditions for the remainder of life. Protein is cited as a current example, but

all the dietary constituents need to be studied in this manner. The same statements that have been made about protein might be made about sodium chloride, or calcium or vitamin A as well as numerous other substances.

Sherman and Campbell (38) have compared the effects of two different diets upon the life activities of large groups of rats. They have found that a diet that may be sufficient to permit growth and reproduction, such as a mixture of wheat and dried whole milk in a ratio of 5:1 with one per cent of salt, can be improved by increasing the milk to one-third of the mixture. By such improvement they found the number of young produced and the length of life of the animals were both increased. From their experiments it is evident that one diet is inadequate compared to the other if we consider an adequate diet as one that permits the optimum in life activities. This optimum needs to be measured in several different terms, such as length of life, freedom from disease, and reproductive activities.

In an extension of this early work Sherman, Campbell and Rice (39) supplemented the diet of wheat and milk (5:1) with calcium carbonate, butter fat and dried skimmed milk. The first two were employed both as single additions and in combination.

The rate of growth was improved by the addition of calcium or dried skimmed milk. These supplements also produced a more efficient utilization of feedstuff as measured in terms of body weight produced from a thousand calories. The addition of skimmed milk also produced slightly more rapid growth in the early age period and slightly larger animals in the end.

In the case of the females the period of producing young was longer and larger numbers of young were born and reared upon the diets supplemented with calcium or butterfat. Slightly earlier maturity resulted from feeding skimmed milk or calcium. Eleven per cent of the females were sterile upon the original diet and 20 per cent failed to rear young. All supplements improved this condition.

Observations made in the course of these studies indicated that the animals receiving the supplement of skimmed milk were superior in firmness of body and condition of the fur coat during youth and early adult life. The addition of butter fat to the diet seemed to give a softer hair, while those fed calcium supplements seemed to retain their youthful appearance longer.

None of the large number of rats used in the above experiment, as far as reported, lived to the ripe old age of those in Slonaker's early experiments nor did any have a length of life comparable to the oldest in the retarded growth experiment made at Cornell. It is possible, but unlikely, that breeding is a factor here. It seems more likely that factors such as growth rate are able to overbalance minor dietary improvements.

Sherman's data indicate a useful type of experiment in which a given dietary is improved from the point of view of the entire life activities instead of from a single consideration such as growth rate. In past problems of nutrition, it is possible that growth rate had been accepted too readily as a proof of a better diet. In the future it may prove desirable to develop slower growth rates with improved life span activities such as reproduction and length of active middle life.

In the second study of Sherman and coworkers there was no general correlation between growth rate and life span. They found the life span was greater in the animals whose early growth rate had been slowed by the supplement of butter. On the other hand, the life spans were also greater for the other supplements that had resulted in an accelerated growth rate Such experiments are dealing with deficiencies and the results are probably

TABLE 2

Mean length of life in days found upon adding various supplements

(Sherman)

Diet enrichment	None	Calcium	Butter fat	Calcium and butter fat	Skimmed milk
Males	658	703	667	689	681
Females .	723	746	818	739	754

too complex to permit conclusions concerning the interplay of the two factors of growth and life span.

Chen (40) attempted to study the effect of beef proteins upon the length of life. He concluded that beef protein tended to shorten the life span. However, his diets were poorly designed and the number of animals too small to permit true conclusions.

Campbell and Sherman (41) have supplemented their diet of milk and wheat (1:2) with meat and green beans. This resulted in a more rapid early growth, earlier maturity and attainment and maintenance of larger adult size. It did not increase the life span.

In the past all nutrition research has centered its efforts upon the first half of life. In spite of the importance of the latter half of life in human well-being this field has been neglected. The results of eight years of experiments covering the latter half of life in regard to nutrition experiments with white rats have appeared (42).

These studies have attempted to get preliminary answers to the problems of the value of exercise in later life, the dangers of becoming overweight, the amount of protein that should be consumed and the quality of protein that should be eaten for promoting optimum health in later

life. Rats were used in these studies that had been kept for about a year, or half of their lives, upon a good stock diet. At middle life some were fed diets rich in protein and others, moderate or low protein diets, some were forced to run in rotating cages daily and others were not, some were allowed to grow fat, others were kept thin, some were fed protein from meat, others from milk.

The results of these studies indicate that the degree of body fatness in later life is more important than such variables as protein or exercise. Rats that become very fat have shorter spans of life than those that are obliged to remain about ten per cent lighter in body weight. On the other hand, rats that are unable to fatten on good diets and tend to remain underweight live shorter lives like the overweight rats. This question of body weight dominates all other variables such as the protein level, the quality of protein or exercise.

The effects of different levels of protein were studied in a series of experiments. High protein produces larger kidneys and higher non-protein nitrogen in the blood, as others have found. When animals die, the kidneys show signs of somewhat more injury upon the higher protein diets but there is no evidence that this foreshortens the span of life. Since so much of the life of older rats centers around the condition of the lungs, perhaps the rat's life span is less dependent upon the condition of the kidney in old age than is that of man.

In these as in other studies of exercise at Cornell care was taken to train the animals by short periods of running at the beginning. Even under these conditions some rats with diseased lungs were killed in a few months by the exercise. On the other hand, healthy ones seemed to survive longer as a result of the exercise. The mean span for all animals was not affected since those killed prematurely neutralized the favorable effect upon the healthy. Benedict and others (43) exercised rats in middle age without previous training and found they killed the males prematurely but benefitted the females. This sex difference was probably due to the greater mean life span of females and consequently these researchers were dealing with physiologically younger animals.

In consideration of combined factors the favored group for long life was the one maintained during the latter half of life with exercise, not fat, upon a low level of protein, with this protein furnished by liver.

Very few data are available from studies with animals for human guidance in such nutritional problems as the amount of roughage to eat to insure good evacuation of the bowels, how much water to drink, how many extra vitamins to consume and what specific foodstuffs to avoid.

The best writers on the subject of health and longevity such as Sinclair (44) have stressed the importance of the functioning of the intestine. Over

a century ago Sinclair stated "Costiveness has a dangerous tendency and it is desireable to rectify it." "*A costive habit may be removed by certain* articles of diet such as roasted or boiled apples, pears, stewed prunes, raisins, butter, honey, sugar and such like."

Levels of cellulose up to twenty per cent were fed to rats in small numbers throughout life. The span of life upon the high cellulose diets was equivalent to the best usually found after normal growth (45)

Hoelzel has devoted a lifetime to the study of various forms of bulk in

TABLE 3

Level of dietary cellulose and life span of rats (45)

Diet	Number of male rats	Mean age
		days
Stock	75	503 ±12
Stock plus 10% Cellulose	8	674 ±35
Stock plus 20% Cellulose	9	602 ±61

TABLE 4

Life span of rats and bulk in diet (44)

(Number of rats in parentheses)

Diet	Males	Females
Basal (⅔ meat)	630 ± 90 (14)	780 ±196 (12)
5% bulk	795 ±192 (8)	873 ±116 (7)
10% cellulose	782 ±156 (8)	626 ±119 (7)
Vegetarian-meat	813 ±223 (4)	836 ± 91 (5)
Vegetarian meat	538 ± 38 (2)	482 ±146 (2)

the human diet. Recently he reported some life span studies with rats (46). The results are summarized in table 4.

In spite of the great variability of the data, these results seem to indicate a favorable trend as a result of the bulk in the diet.

The craving for bulk seems to differ between rat species. Without bulk cotton rats will die prematurely with their stomachs clogged with hair while albino rats under the same conditions will thrive without signs of hair balls (47). However unpublished data from the Cornell laboratory indicates that white rats maintained throughout life upon diets of liquid milk will show a substantial number having balls of hair in the stomach at the time of death. Control rats fed diets containing natural roughage had no hair balls. It is not known whether the milk diet stimulates the eating of hair or whether the bulk materials in a stock diet sweep hair through the gastro intestinal tract.

Many natural products such as apples, the peelings of citrus fruit, bran and other forms of bulk are available to man. Each individual seems to have his own level of need and response to irritation from fiber.

Little experimental study has been given to the effect of the ingestion of different levels of fluid upon longevity and old age diseases. Some clinicians find an increased intake of water during the later years of life to be useful in relief of constipation and in general improvement of well being (48).

Some years ago Anheuser, Busch and Company ran extensive tests with rats. They compared beer containing 5% alcohol, dealcoholized beer, distilled water and a 5% solution of alcohol in water. They found no difference in span of life. The mean life span for both males and females in all groups was between 21 and 22 months while the mean reproductive span for the females of each group was 15 months without significant variation.

TABLE 5

Fluid consumed at age of 6 months and mean span of rats given various liquids

(Cornell data, unpublished)

Liquid	Life span (days)		Fluid drunk (ml./100 gm. body wt.)	
	Male	Female	Male	Female
Water	509 ±16	618 ±21	6	8
Milk .	502 ±21	613 ±22	30	32
Coffee	530 ±21	598 ±22	8	9
Sugar	521 ± 9	654 ±20	20	18

The mean daily liquid consumption of these rats at the age of 4 months varied from 25 to 31 ml. for the males and 20 to 26 ml. for the females. In each case the lowest values were found for the water drinkers. Since the basal diet was well planned and probably more than adequate the ingestion of calories in the form of alcohol had no effect on the life span or reproduction of the rats.

In the Cornell laboratory coffee has been studied in tests with rats. In the initial study it was found that coffee fed in moderate amounts as a beverage had no effect upon the life span. Three generations of rats were reared with no other fluid than coffee (49). In a later study four sources of fluid were compared namely, water, 10% sugar solution, coffee and whole milk. The last group was given no food except the milk although traces of Mn, Cu, Fe and I were added. The other three groups were fed a high quality mixed diet known to be adequate. The sugar solution was used because rats are very fond of it and will drink large amounts. The amount of fluid consumed and the mean life span in days is given in table 5.

These results must represent comparisons between moderate and high levels of fluid consumption throughout life. Even the lowest values represent about 2% of the animal's body weight which would correspond to the 3 pints of fluid daily for a man.

These data indicate no favorable influence upon the span of life of high levels of water. Furthermore they indicate that the rat adjusts itself to coffee since there is no evidence of increased consumption resulting from diuresis. In the case of the milk fed rats the feces were well formed with no indication of diarrhea. This subject deserves much more study, since the water balance of the body plays such an important role in the body during the later period of life.

The effect of supplementing human diets with vitamins has been given little attention in terms of effects upon the span of life. For some years synthetic vitamins have been added to the white flour and bread produced in the United States but most evidence indicating favorable results in terms of better health has been questioned because increased incomes have permitted additional purchases of meat, milk, eggs, fruit and vegetables by the American public during this period of "enrichment" of flour and bread.

Little study has been given to the effect of the fat soluble vitamins upon the total span of life. In one study with rats Paul and Paul (50) found the span of life increased progressively as they increased the vitamin A allowance from one to twenty units per 100 gm. of body weight. At the highest level the mean age at death was 622 days for the males and 675 for the females.

The studies of Sherman and others (51), however, would indicate that there are upper limits in which vitamin A begins to injure the animal body. Levels of 12 and 24 units of vitamin A were compared. The lower level of vitamin A was more favorable when measured in the white rat in terms of reproductive life of the female, number of young born and reared as well as weight of young at the time of weaning. There was even some evidence of the shortening of the span of life by the higher level of the vitamin. As these rats grew older the level of vitamin A in the liver increased. At 700 days of age the livers of the females fed the higher level of vitamin A contained over 3,000 units of vitamin A per gram of fresh tissue. Sherman notes that this level is about one fourth that found in the toxic livers of seals and polar bears.

In a study of the carotene and vitamin A values in the plasma of a group of older patients, wide variations were found but no evidence of deficiency. Unfortunately no attempt was made to correlate diets of individuals (52). However many older people have low values for vitamin A in the blood serum. Among 27 normal older people, two-thirds had fasting levels below

40 γ/100 according to Rafsky and Newman (53). Likewise the serum carotene levels were low. Feeding vitamin A or carotene produced normal values.

No evidence has been found that vitamin D exercises a favorable effect upon calcium assimilation in old age. Old rats ranging in age from 104 to 110 weeks of age were held at food levels of 0.3 and 0.5% calcium by Mrs. Kane, a student from India, working at Cornell. She found the calcium balance in these old rats was the same whether she fed 4 or 40 International Units of vitamin D per gram of feed. Possibly even the lower limit was adequate (54).

TABLE 6

Estimates of nutrients consumed by older people

	Rackow		Pyke		Ohlson	
	Men	Women	Women	Men	Women	Women
Calories	2,653	2,103	1,434	2,160	1,316	1,906
Protein (gm.)	90	68	68	107	75	67
Fat (gm.)	93	76	24	69	91	
Carbohydrates (gm.)	364	287				
Ca (gm.)	1.07	0.87	0.5	0.8	0.6	0.66
P (gm.)	1.60	1.22				
Fe (mgm.)	18	13	8	15	7	
Vit. A (I.U.)	8,932	5,143	2,500	3,600	1,450	
Vit. B_1 (mgm.)	1.9	1.2	0.7	1.4	0.8	
Ribo. (mgm.)	2.5	1.8	0.8	1.3	0.9	
Niacin (mgm.)	17.4	12.7	7	16	7	
Vit. C (mgm.)	76	65	12	33	16	
Vit. D (I.U.)			74	90	101	

Marginal levels of vitamin E in the diet lead to premature sterility in male rats but this does not seem to be related to the span of life. Even in man no one has shown that early sterility is associated with a shorter span of life. In experimental animals such as the rat, it has been assumed without evidence that the later the menopause in the life of the female the greater the span of life. In the Cornell rat colony the oldest female to produce a litter and rear it was a rat 25 months of age. Others have found in rats with a mean reproduction span of 15 months that the extremes for various diets were 20 to 22 months. Vitamin E may play an important part in maintenance of muscles during old age but no one has provided experimental evidence to support this hypothesis.

In one of the studies of von Euler (55) a group of rats were given an extra supplement of 500 γ of "vitamin E" but this had no effect upon the span of life.

The lack of vitamin E in the diet of female rats will produce sterility. After a long period of 22 months the hind legs will also become paralyzed. Thus it requires a long continued deficiency to injure the muscles in old age (56). In the case of herbivora, however, *the injury to the muscles including those of the heart, is quite rapid* (57).

Few attempts have been made to evaluate diets eaten by older people. Rackow (58) studied a group of senile patients in one of the mental hospitals of New York State. This hospital offered an unusually liberal diet. Pyke (59) studied two homes for aged women and one for older men leading an active life. *Pyke considered the intake of vitamin A by the women* studied as too low. The American study took place during a period of national food surpluses while the British estimates were made during one of shortage (table 6).

TABLE 7

Data from Drummond indicating the favorable influence of wheat germ upon the life span of the white rat

Colony differences seem more important than dietary ones

Diet variable	Sex	Mean span in weeks	
		UC colony	VL colony
Wheat germ	Male	84	116
None	Male	64	88
Wheat germ	Female	85	104
None	Female	73	92

Vitamin C

The levels of vitamin C would seem to be adequate for those studied by Rackow and inadequate for the British women. The trend has been for the Americans to set 75 mgm. of ascorbic acid as an adequate daily allowance while the British have claimed one third this amount might be sufficient. In a large institution Horwitt found 50 mgm. daily was adequate (60). Bouton (61) has found some eye conditions in the aged to improve upon feeding vitamin C. Most of these patients had been living upon a diet rather low in this essential.

Water soluble vitamins

In 1938 Drummond attempted to compare groups of rats fed two levels of water soluble vitamins. The chief variable was introduced by the replacement of white flour by 15% wheat germ in one diet (62). Rats survived longer *when the diet contained the wheat germ. The life span data* are reproduced in table 7 since the rats kept in one colony survived much

better than those in another. This indicates variability that can enter such research independently of the dietary factors.

Various attempts have been made to feed rats diets consumed in certain areas in order to determine the effect of long continued consumption following a given food pattern. Usually the factors involved in such tests are the water soluble vitamins although protein and minerals may also be implicated.

In India, Robert McCarrison (63) fed groups of rats diets typical of various areas of the country. The poorer diets produced a high rate of premature deaths as well as mediocre physical development. These studies are often cited by those who advocate reduction to a minimum in the processing of human foods such as wheat.

Orr and associates (64) attempted to compare a diet typical of that eaten by the Scotch people with a similar one supplemented with milk and vegetables. In terms of life performance, the supplemented diet proved much superior from the point of view of growth rate, life span and reproduction. The results are similar to those of Sherman, probably due to the same reason, namely, an inadequate diet at the beginning. This experiment also permits no conclusions concerning the relationship between growth rate and life span because the animals were probably suffering throughout life from manifold deficiencies which not only slowed the growth rate, but shortened the life span. If growth rate and life span are to be studied as related factors, the lowered rate of growth can be produced better by a single deficiency which is made good after the animals attain adult size.

One study has been made by Sperling and associates (49) in which a large group of rats were fed from birth until natural death upon a food mixture resembling that consumed in the northeastern section of the United States. The mixture fed, consisted of fresh eggs, 3, whole dry milk, 4, margarine, 2, butter, 2, hamburger, 10, pork sausage, 4, white bread (not enriched), 16, potatoes, 31.7, tomatoes (canned), 3, Navy beans, 1, fresh carrots, 7, apples, 10, salt, 0.3, and sugar, 6. The potatoes, meats, eggs and beans were cooked.

A second group was fed this diet and given in addition a weekly supplement of vitamins as follows: vitamin A, 840 I.U., thiamine 300 γ, pyridoxin 300 γ, riboflavin 20 γ, pantothenic acid 550 γ, nicotinic acid 4 mgm., "filtrate factor" 54 units. The mean span of life for these rats was similar to that of the group fed the diet without the supplements. This casts doubt again upon the merit of "enriching" flour or bread with three synthetic vitamins.

A third group of rats was fed a modified form of the basal diet which contained liver, more milk and whole wheat bread. This also led to no increase in the span of life.

If the rat provides a criterion for human guidance these data indicate that the average diet is adequate. However such a conclusion leaves out of the picture the substantial number who consume a large fraction of their foods in the form of sugar, white flour, alcohol or fats.

In studies with rats from weaning until old age Mills (65) found that [illegible] vitamins that was needed [illegible] believed older patients profited from additional [illegible]

Selected diets were fed by Horwitt to groups of patients (67) in a large hospital. The diets provided daily, 2200 calories, 400γ of thiamine and 900γ of riboflavin. These allowances of water soluble vitamins proved to be too low and led to irritability and restriction of activity by the patients. Recovery was rapid after feeding yeast extract.

Dry brewers' yeast seems to be one of the most useful foods for older people. It provides an economical supplement of protein and water soluble vitamins. It helps prevent constipation. If taken as a teaspoonful stirred into water before meals it helps prevent overeating by those with excessive appetites. It may disagree with patients who have a tendency toward gout since about one fifth the nitrogen of yeast is found in the form of purines.

Evidence to show specific dietary effects upon the course of development of degenerative diseases in man is difficult to obtain. Langstroth (68) has presented clinical evidence of the beneficial effects of diets richer in vitamins and poorer in purified foodstuffs. Such evidence is open to many criticisms, but probably is the best available today.

However all evidence indicates that the typical older person who avoids obesity eats very little food. This must be carefully selected from such products as milk if the body is to be provided with even a marginal allowance of essentials such [illegible] calcium and protein. All ages need to be careful that the intake [illegible] and white flour is kept low; in [illegible] calorie intake are low, such care is essential.

Protein

For more than a century students have given much thought to the amount of protein needed in the body of a growing child or animal since the muscles, soft tissues and even the bones are built from a structure of protein. For seventy-five years it has been known that proteins differ greatly in quality. For a century and a half it has been recognized that a protein such as gelatin is very poor in quality while the white of an egg is very rich. If the whites of eggs were made of gelatin, the bodies of baby chicks could never be created within the egg.

Since proteins have different composition in terms of amino acids and since quality depends upon these amino acids, several proteins combined and eaten at the same time are often far superior in quality to the same proteins eaten individually. Poor quality bread made from white wheat flour is much inferior in its protein quality to a bread containing milk, soy flour and wheat germ. The body also derives more value from the protein if these different ingredients are combined into one loaf than if a man eats poor quality white bread at one meal and drinks milk alone for the next.

The needs of the adult for protein remain uncertain even today. At the end of the nineteenth century, a few dominant personalities nearly convinced the civilized nations that a high intake of protein was desirable. They fixed the amount to be ingested daily as 100 grams or more. Shortly after the turn of the century, however, this level was severely criticized by Hindhede (69), Fletcher, Chittenden and others. The present generation, especially in America, has tended to consume more milk proteins but at the same time they have also inclined toward diets rich in vegetables. A few experiments by individuals have attempted to stem this tide in favor of diets richer in meat. Thus a few persons have lived upon diets rich in meat for a period of a year or two. However, their conclusions that such diets are satisfactory for long continued use cannot be accepted without question because their experiments represent too short fractions of the total life span and also because too few individuals have been involved to permit generalizations.

After reviewing the limited literature Pyke concluded that about one fifth of the women studied in England were not getting their requirement which he set at 42 grams of protein daily. Most of the men studied, exceeded an estimated need of 54 g. daily (59).

Nitrogen balance studies by Kountz and others (70) indicate that an allowance of 1.0–1.2 g. per km. of body weight is not sufficient protein for many older people. In some cases even 2 gm. per kgm. was not sufficient. These latter cases resemble people suffering from some injury that tends to throw them into negative nitrogen balance.

In a group of normal and supposedly healthy older women Roberts and others found that nitrogen equilibrium was maintained on 57 gm. of protein daily. Although one woman seemed to require 1.3 gm. of protein per kgm. daily, the other seven needed only 0.7 to 1.0 gm., per kgm. of body weight (71).

The balance studies of Ohlson and associates indicate that 55 to 60 grams of protein daily is a marginal level for older women. A substantial fraction were able to remain in equilibrium on this level (72).

The data of Ohlson provide useful guidance for those who desire to study the nutrition of older people. From a study of 18 subjects she found

a mean protein intake of 57 grams daily based on estimates and 63 grams based on analyses of a ten-day food sample. This is just the opposite from findings in naval messes in which the estimated values were consistently higher than those found by analysis. However in the studies of older people estimates were based on food served while navy estimates were derived from food issued from stores (73).

Ohlson estimated the daily ingestion of protein, calcium, thiamin, riboflavin, vitamin A and ascorbic acid in relation to the calories consumed per day. Women consuming food to provide 1,000 to 1,499 calories ingested 42 grams of protein while those ingesting the level of 1,500 to 1,999 calories daily obtained 55 grams of protein. The importance of the use of substantial amounts of milk with little sugar and white flour is indicated in the case of four women studied who were over 70 years old and ate only 1,500 calories daily. By the careful selection of diets they ingested 55 to 60 gm. of protein daily. In contrast five women with poorly selected diets were in negative balance for essential nutrients even when they consumed 1,600 calories.

In one of a series of articles dealing with the practical problems of middle age, Comrie (74) has discussed the diet. He advances little beyond the concepts of Cornaro. However, he states it in modern terms advising the man doing hard work to consume about 3,000 calories while the working woman eats food to provide 2500. He advises much less in sedentary occupations. He observes that men tend to overeat in regard to meat and women in amount of pastries.

The attack upon the protein problem can probably be made to best advantage today by long period studies with omnivorous animals such as rats and dogs. After sufficient clear cut evidence has been gained from such experiments there is no reason that demonstrations cannot be made with groups of people. No one can state today the amount of protein that an adult should consume.

If rats have an adequate basal diet there is no evidence of premature old age or shorter span of life when the diet is supplemented with liberal amounts of protein in the form of milk or meat (49). Sherman found no increase in life span of rats when he increased the protein level of his diet from 16 to 20 per cent by the addition of meat to a milk-wheat diet (75). However the reproduction in terms of number of young produced and reared did increase with this additional allowance of meat. The performance may have been a reflection of some factor such as vitamin B12 since meat was used for this study instead of pure protein.

Protein level in the diet is reflected quite readily in the weight of the kidneys and the blood urea level. McKay (76) fed middle-aged rats upon three levels of protein. These were placed upon the diets at 346 days of

age and killed at 400 days. The diets contained 18, 31, and 67 per cent protein. Each group of rats consumed about the same number of calories per area of body surface. The rapid response of the blood urea and kidney weight was evident even in this period of 54 days.

The effect of protein upon these middle-aged rats was much less than upon growing ones. This result was explained later.

This enlargement of the kidneys is a response to the blood composition and is the result of both *hyperplasia and hypertrophy* of the kidneys. The kidneys of adult rats respond in even one week to a high protein level in the diet. After removing one kidney from rats Smith and Moise (77) found the other to be 5 per cent enlarged after 3 days and 48 per cent after 150 days. This increase is proportional to the protein level in the diet. The dry material of the kidney increases showing that water was not responsible for the enlargement.

Later McKay and McKay (78) took account of the higher ingestion of protein by young rats and thus explained the more marked effects upon the kidneys of young than upon old ones. For this same reason McKay concluded a diet with 1 per cent cystine may be toxic to growing rats and not very injurious to the kidneys of adults.

Rats over 60 days of age excrete more albumin if fed a high protein diet. At 350 days of age rats fed Sherman's A and B diets usually have intact kidneys, but at 500 days of age on these same diets spontaneous focal lesions become common (79).

Renal enlargement is not produced in rats by feeding urea in amounts equal to protein so the cause of the enlargement is somewhat obscure (80).

The kidneys of rats fed high protein diets throughout life were studied by Blatherwick and Medlar (81). In a diet made rich in protein by including seventy-five per cent liver, the mean life span for both sexes was only 506 days. There was marked injury of the kidneys, especially in nephrectomized animals. Female rats were more refractory to the production of nephritis than male ones. The addition of desiccated thyroid to the diet of the females that had been nephrectomized favored the development of nephritis. A diet containing seventy-five per cent of casein also injured the kidneys but the action seemed slower than in the case of similar liver diets.

These life span studies of Blatherwick and Medlar (81) are also interesting inasmuch as they found diets containing five per cent of irradiated yeast developed marked calcification of the kidneys and aortas as well as renal calculi in a hundred per cent of these animals. The mean life span of the rats used in all their studies was relatively short, however, but no explanation seems available.

For some years the problem of kidney calcification has attracted attention in the Cornell laboratory because factors of diet, age and sex seem

involved. X-ray photographs are made of the kidneys of all old rats at the time of death.

In the course of study of manganese in the diet completed in 1941 Barnes observed that the kidneys of female rats tended to have a higher incidence of calcification than those of male rats.

In later studies in which a constant but restricted allowance of an adequate basal diet was fed to a group of rats, retarded in growth, while four additional sources of calories were fed to rats allowed to grow normally, the sex difference in kidney calcification was very marked among the normal animals (21) (table 8). In this study there was a very low incidence among the retarded animals in spite of their much longer span of life.

TABLE 8

Incidence of calcium deposition in kidneys (21)

Diet supplement	Females		Males	
	No. of kidneys	Incidence %	No. of kidneys	Incidence %
Starch	38	21	40	5
Starch-sucrose	31	12	36	8
Starch-milk	38	45	38	0
Starch-liver	38	61	38	29
Basal (retarded)	124	6	126	5
Milk	46	98	44	68
Water	46	87	40	13
Sucrose soln.	48	77	46	33
Coffee	46	93	40	23

In a later unpublished study in which the basal diet was constant for three groups and a fourth group was fed only mineralized milk, the sex difference in kidney calcification is also marked (bottom of table 8).

In the earlier studies there seemed to be little correlation between kidney calcification and age at death while in the last study the incidence increased regularly with age at death.

The retardation in the growth of rats does not inhibit the calcification of other soft tissues as it does the kidneys. Among normal male rats over 500 days of age at the time of death, the calcification of the tubules and spermatic artery of the testes occurs in 80 to 90 per cent of the animals. Among retarded rats this incidence is found after the males are 800 days old. The calcification occurs at a later age but in the older rats is just as severe. The results are also about the same in the tissues of the heart which shows about the same incidence as the testes.

When the data from the lower section of table 8 are considered on the basis of age and sex without regard to the four liquids consumed, the sex difference persists indicating that females have a higher incidence of kidney calcification independently of the age at death. In other words the female

TABLE 9

Age and incidence of kidney calcification

(Liquid expt. 1950)

Age	Male		Female (virgin)	
	No examd.	% calcified	No examd	% calcified
days				
399	26	27	12	67
400–499	28	25	22	91
500–599	60	40	43	79
600–699	36	36	32	88
700–799	22	36	38	95
800–899	2	0	20	100
900–961	—	—	16	94



[illegible] The tumor

[illegible]

of Elliots.)

does not develop more kidney calcification just because it lives longer (fig. 5).

Dietary lipids

The fondness of older people for fat during the later years of life has been the subject of frequent comment (82).

Few studies have been made concerning the effects of different lipids

upon the span of life. The comparative effects of butter and margarine when fed throughout the life of the rat were studied by von Euler (55) No differences were found. The rats in Sweden had about the same span of life and died with the same diseases as they do in America.

Okey (83) fed rats diets containing one per cent cholesterol throughout life. She concluded that their growth, health and time of survival did not differ significantly from control animals fed the same basal diet without the cholesterol. These studies have added interest today when some clini-



FIG 6. Rats from a retarded growth experiment after they had attained an age of 1320 days, equal to about 132 years for man. "He is deformed, crooked, old and sere, ill-faced, worse bodied.'

cians attempt to maintain patients upon low cholesterol diets in the treatment of athersclerosis.

Three practical considerations concerning fat in the diet of older people are worthy of study. In the first place if the daily calorie allowance is low while the amount of fat consumed is high, the diet may become very deficient in essentials such as vitamins, protein and calcium. In the second place fat may cause the wastage of dietary calcium. In old rats the wastage of calcium is proportional to the amount of fat in the diet. The more fat in the diet, the greater the loss of calcium (54). In these rat studies Kane also found that hard fats produced more wastage of calcium than soft ones. Thus tallow produced more loss of calcium than butter fat. These relations between calcium and fat do not hold for young or middle aged rats. No one has studied this problem in man.

Some old people tend to restrict their fat intake, according to the obser-

vations of Meyer (84). During periods of high prices for meat and fats, the allowance of dietary fats may be low in the institutional feeding of the aged. Careful programs of fat salvage may increase the level of dietary fat in such institutions. In 1948 after instituting a program of fat conservation, enough fat was saved to increase the daily allowance of all patients by about twelve grams, in N. Y. State mental hospitals.

In practice the consumption of fat by old people is probably an individual problem. In some cases the amount of fat eaten should be curbed and in others it should be increased.



FIG. 7. Extreme old age. This was the last survivor in an experiment to determine the effect of the level of protein ingested upon the span of life.

Minerals

Among the inorganic substances there are only a few that need to be considered carefully during old age or most other periods of life. These are iron, iodine, sodium chloride, and calcium. Little attention has been devoted to the first three but substantial attention has been given calcium during the past twenty-five years.

The trend toward decreased consumption of foods rich in iron by older people in this country as well as the decreased acidity of the gastric juice emphasizes the importance of iron in the diets of older people. Furthermore the richest sources of vitamin B12, which contains cobalt and is essential for hemoglobin formation, are animal food products such as meat which tends to be eaten in small amounts by older people. Stieglitz (48) emphasizes the importance of iron, on the basis of his clinical observations of older people. On the other hand in England Howell (85) finds little anemia among older people.

The need for iodine in later life is little understood. The decline in basal metabolism may be a protective mechanism of later life. Increasing this

metabolism by use of thyroxin or iodized proteins may not be in the best interests of the aged.

The extensive use of low salt diets in the treatment of hypertension introduces many problems concerning the maintenance of equilibrium among the electrolytes and water within the bodies of older people. Little research has been devoted to the salt requirements of more normal older people or animals.

Calcium

The human interest in calcium centers at the opposite ends of the life span. The young desire to develop strong bones. The old hope to maintain the bones and avoid the common broken hip.

Between the animal nutritionist and the specialist in human nutrition, the attitude toward an adequate allowance of calcium is very different The human diet is usually considered adequate in calcium if it provides a gram per day or about 0.2% of the food on a dry basis. Animal diets are usually designed to have at least 0.5% calcium.

Some of the basic problems concerning calcium during later life are: the assimilability in relation to the form of calcium in food, the effect of other food factors upon calcium utilization and changes in calcium assimilation with age. These important problems are solvable by using well established methods such as chemical balances and newer techniques employing radio active Ca 45.

Owen (86) after running calcium and phosphorus balances upon 10 male subjects concluded the requirements were about the same for old and young adults. Individuals remained in equilibrium upon an intake of about half a gram of Ca and 1.2 grams of P daily.

The amount of calcium stored in the case of young growing animals is known to reflect the previous adequacy or deficiency of the diet in this element. Little is known about such factors in the case of adult man. However Clark (87) found quite a continuous storage of calcium in his study of San Quentin prisoners during a period of 28 weeks. This might reflect a long standing deficiency of the prison diet in calcium since Clark believes there was no error due to discarding fecal samples.

From balance studies with a group of older women, it was concluded that a gram of calcium per day was needed (71).

More recently Ohlson reported (72) that a group of older women could be kept in calcium balance with a daily intake of 0.7 to 0.8 gram. This is probably a rough marginal requirement that will need to be modified for each individual and for the form of calcium salt consumed.

In human studies little attention has been devoted to the form of calcium contained in the diet. This may prove very important. Probably as

much as half of all the calcium in American bread today is in the form of calcium sulfate. This is introduced as a carrier for bromates under the name of yeast food. Most of the remaining calcium is put into bread in the form of dry skim milk. Milk calcium is known to be well assimilated at all ages but this is not known for calcium sulfate.

The most difficult forms of calcium to assimilate are commonly supposed to be those that occur as oxalate in plants such as spinach and the calcium phytate formed by the combination of the phytin of bran and the calcium of bread. Nevertheless studies with rats indicate that during the middle period of life even calcium oxalate is well assimilated while in the period immediately after weaning or the last third of life, calcium is not well utilized in the presence of oxalate. Furthermore if calcium is consumed at



FIG. 8 Female rats outlive males. This animal reared a litter when 24 months old.

one meal and oxalate at another, the assimilation of calcium is better because there is less chance of forming the insoluble calcium oxalate in the stomach (88).

Studies with old rats and old dogs indicate that the body tends to lose its calcium when the animal starts the last third of life (fig. 9). In all cases in animals this loss can be partly or entirely prevented by adequate dietary levels. The post menopausal loss of calcium in women has been given much attention by the clinician but little consideration by the nutritionist (89). This loss occurs at an age comparable to a fifteen months old rat or eight year old dog.

Many food factors probably affect the assimilation of calcium. In young animals phosphate may be tied up and lost due to the presence of surplus calcium in the diet. However, surplus phosphorus which is common in human dietaries does not seem to waste substantially the calcium, at least in the case of young animals (90).

Both the level of fat in the diet and the hardness of fat influence the assimilation of calcium in old animals such as rats but these lipid factors seem to have influence in the case of young animals or middle aged adults (54). The more fat in the diet and the higher the melting point of this fat the more the wastage of calcium during the latter third of life.

The absorption and utilization of calcium and iron need to be considered in relation to such factors as the lowered secretion of gastric hydrochloric acid during the latter years of life.

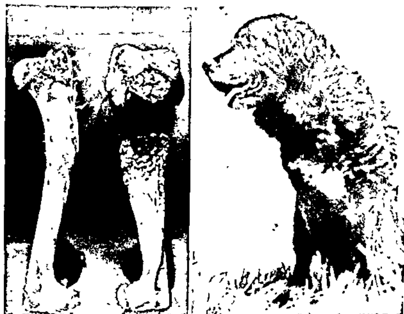


FIG. 9. Aged Newfoundland long in negative calcium balance died with this broken leg.

However, in the case of very soluble forms of calcium such as that found in milk, assimilation from the gut seems rapid both early and late in life. After such calcium reaches the blood its removal either by deposition in bones or excretion is much slower in the case of old animals than it is in young ones. This slowness of removal from the blood may be related to declining kidney function or to reduced secretion from the salivary and pancreatic glands.

Unpublished studies using radio activity calcium indicate that calcium fed in the form of the lactate is rapidly absorbed. The blood contains a substantial amount even when the calcium is fed dissolved in milk. At the end of about 4 hours the blood level reaches a peak in Ca^{45}. In the case of young dogs this level declines very rapidly within 24 hours while in

the case of old dogs a substantial amount of the radioactive calcium can still be detected in the blood at the end of six days. These differences have not been explained and tests have not been made with human beings (fig. 10).

The problem of the effect of various levels of calcium upon the total span of life has been given limited attention in studies with experimental animals. In studies with rats fed a diet similar to that eaten by man,

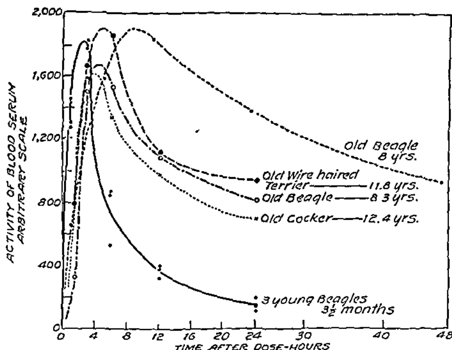


FIG. 10. Radioactive calcium[45] enters the blood stream rapidly after being fed but leaves more slowly in old than in young dogs.

Sperling could find no benefits from the addition of calcium, in terms of length of life (49). Likewise Shields and Mitchell found no advantage in additions above the 0.2% level which is now considered optimum for man. However Van Duyne and others found beneficial effects from increasing [illegible]

tic animals, so one cannot make application of findings on such diets in applied nutrition (9). However, in the light of a wide variety of animal experience, the conclusions of Sherman that man needs more dietary calcium are well justified.

This problem of calcium in the diet of older people has been reviewed in more detail elsewhere (82).

Metabolism

An excellent review of early metabolism studies in old age was published by Robertson in 1907 (92). A few of the European studies of a half century ago can still be read with profit. Fenger ran balances upon a woman who lived for 15 years on a very frugal diet which allowed only 1125 to 1600 calories daily (93). Koch also ran balances upon a group of older men in Finland without finding outstanding differences (94).

Basal Metabolism

The decline in the basal metabolism of man in the course of ageing has been recognized for a century. One of the best of the earlier studies was that of Sonden and Tigerstedt (95). Individual values vary widely. In a study of 15 older women, the basal calorie expenditure varied from 1,130 to 1,735 with a mean value of 1,367 (72). Three women in the 70's expended 1,195, 1,402 and 1,504 basal calories respectively. From earlier literature Pyke estimated that old women in England had a basal need of 1,100 calories per 24 hours and old men needed 1,400 calories (59). To this he added 10% for specific dynamic action. With modest activity he concluded older women needed 1,700–1,800 calories while older men needed 2,200–2,300.

TABLE 10

Decline of basal metabolism with age in women (97)

Average 35 to 40 yrs	*33 8 calories per sq m per hour*
40 to 50 yrs	33.4 calories per sq m. per hour
50 to 60 yrs	*31 0 calories per sq m. per hour*

In terms of calories per square meter of body surface per hour the basal metabolism drops steadily in the case of man until the age of about eighteen. After this there is a slow but steady decline according to DuBois (96). The basal metabolism is higher for the male throughout life. During the middle third of life the downward trend of the curve for the female is slight compared to that of the male. The rate of decline for women is shown clearly in McKay's data (table 10) (97).

DuBois (96) has summarized the available data for people over sixty. As one would expect there is great variability due to the degree of senescence. Thus the Japanese found one man, age 93, with a figure of 34.1 cals. per sq. m., and a woman, age 75, with a value of 26.5.

The basal metabolism of eight women ranging in age from 77 to 106 years and for 14 men ranging from 74 to 92 was measured by Matson and Hitchcock (98). No correlation was found between the basal metabolism and degree of senescence.

Those data may be considered to represent the final stages in the life cycle. They show the ends of the curves which have been traced upon a few subjects by Benedict (99) who even noted the decline with advancing age during the period of middle life.

In the case of adult dogs Kunde and Norlund (100) could find no change in basal metabolism with advancing age. They state: "the basal metabolism of 4 grown adult dogs, housed in the laboratory from 2 to 12 years, shows no decline as a result of the advanced age, when living under conditions of moderate amounts of daily exercise and a high protein diet."

The basal metabolism of about a hundred rats was followed by Benedict and Sherman (43) from middle age until death. The total heat production of the same individuals tended to decrease very slightly with age and the body weight also decreased leaving the authors rather perplexed in interpreting results. On the basis of weight alone the old rats had a higher basal metabolism when compared with middle aged rats. The body temperature tended to decrease by about 2°C. in rats more than 800 days of age. One has no means of evaluating the effect of disease in these old rats that were studied.

Black (101) found that age, exercise and protein level in the diet all modified the basal metabolism. In rats over 700 days of age a high protein intake was associated with a high basal metabolism. In animals of equal weight a higher basal metabolism was found in the older ones. Horst and others (32) working with a very limited number of rats concluded that the basal metabolism remained constant during the second and third years of life. Only one of each sex in her experiments attained an age of 900 days so the data for the third year represent only the first half.

An attempt to relate basal metabolism and age in white rats was made by Will (33). She used the technique of growth retardation to produce very old rats. Retarded rats at 850 days of age had a higher heat production per unit of weight and a lower one per unit of surface area than normal old rats. Even at 1200 days of age which is analagous to 120 years for man, Will found no evidence for a decline in basal metabolism. These results may mean that man is unique in undergoing a decline in basal metabolism or it may mean that laboratory rats are dying prematurely from bronchiectasis. In the latter case all workers who have done life span studies with rats have seen only the early part of the span and even a four year old rat may have passed through only the earlier years of a potential span of life.

Changes in Body Composition

"And now I wax old, seke, sory and cold, as muk upoc mold, I widder away."—Towneley Mysteries.

Since very early times ageing has been associated with withering Leeuwenhoek (1632–1723) and Spallanzani (1729–99) were both fascinated by the production of suspended animation in rotifers by dehydration. To them hydration seemed one of the keys to the secrets of life (102).

Modern science has confirmed the early views that senescence is characterized by losses of water from various parts of the body. Today this is a well established phenomenon because it is one of the most marked changes and because the determination is a simple measurement.

In one of the earliest of modern studies von Bezold (103) employed mice, bats, birds, frogs, goldfish and even crustacea. He determined both ash and dry matter in animals of different ages. In the case of higher animals he found development into the adult was associated with a decrease in body water and an increase in ash.

The percentage of water in the brain and spinal cord of rats of different ages was determined by Donaldson (104). From data in the literature he compared the dehydration of the brain of man and rat in the course of ageing.

The brain of an animal loses water throughout life. Donaldson and Hatai (105) compared these water losses in the different parts of the rat brain. There is a very rapid loss until the animal is 30-50 days of age. From this period until 500 days of age, the decline is very slow. The olfactory bulbs tend to maintain a water content of 83 per cent, the cerebellum one of 79 per cent, while the brain stem of the adult averages 72–75 per cent. The oldest rats included in this study were only 530 days of age. This is only the mean life span for a male and these rats can hardly be considered old by modern standards.

In a carefully controlled series of experiments Hurst (106) determined the entire fat and water in the bodies of rats ranging in age from 1 to 112 days of age. Some of these data are shown in table 11.

The female tends to deposit a little more body fat than the male during the period of growth. Both sexes tend to lose water from their bodies at about the same rate. This is a true dehydration and not an apparent effect from lipid deposition in the body.

Even such organs as the eyes share with the body in the general dehydration that characterizes ageing.

The effect of age upon the changes in moisture of the lens and cornea of the eye are shown in the data of Burger and Schlomka (107). These eyes used were taken from cattle of different ages (table 12).

The effect of age upon the composition of cattle was determined by Moulton (108). He found calculations must be reduced to a fat free basis since animals tend to fatten with age. In cattle the increase in body phosphorus, ash and nitrogen is rapid for a period of five months, then it gradually decreases until the animal is 50 months of age. No data were presented

TABLE 11

Water and fat in the bodies of rats of different ages (106)

Number of specimens	Sex	Age	Fat in fresh body		Moisture in the fat-free body	
			Mean	P.E.	Mean	P. E.
		days	*per cent*	*per cent*	*per cent*	*per cent*
6	Male	1	3.0	0.32	85.6	0.40
6	Female	1	3 5	0.15	87.1	0.60
6	Male	10	5.6	0.51	80.9	0.26
6	Female	10	7.4	0.21	80.3	0 51
6	Male	21	5.9	0.19	79.4	0.19
6	Female	21	8.2	0.32	78.3	0.13
6	Male	42	4.4	0.16	76.2	0 23
6	Female	42	4.6	0.08	76.5	0.16
6	Male	112	6 1	0.18	72 9	0.59
6	Female	112	9.2	0.21	72.3	0.23

TABLE 12

Dry matter in lens and cornea of cattle eyes (107)

Lens		Cornea	
Age	Dry matter	Age	Dry matter
0.32	31.5	0.95	14.6
2.3	34.4	1.25	15.4
7.6	35.1	5.45	17.4
12.2	35.8	15.05	18.7
15 5	36 6		

beyond this period. Moulton summarized the earlier studies and concluded that mammals in general show a decrease in water content and an increase in protein and ash until chemical maturity is reached.

Animals relatively mature at birth have a lower water content. Mammals reach chemical maturity at different ages but these are a fairly constant relative part of the total life cycle.

The animal body may vary in fat up to 60 per cent. Swine seem able to store more body fat than herbivora.

The dehydration which accompanies ageing of colloids has led Marinesco (109) to postulate that colloidal phenomena may account for changes in the animal body. He believes that at certain ages, variable with the species, colloidal particles within the body tend to reunite and then cover their surfaces with lipid material. Thus he attempts to account for the granulations of nervous tissue in certain old animals. In old age he visualizes a denser gel with a slower rate of diffusion for crystalloids

The progressive dehydration of cells provides the basis for the colloidal theory of ageing. Ruzicka (110) claims that older cells have a pH nearer the isoelectric point than younger ones. He believes ageing represents passage from a highly to a less dispersed state. The evidence behind Ruzicka's theories is not very convincing. In fact there is considerable conflicting evidence concerning such factors as the change in hydrogen ion concentration of the blood in the course of ageing.

The analogy between ageing in the animal body and in colloidal solutions has been discussed by Wells (111) who shows that in many ways they are similar phenomena.

Dehydration

"But the natural moisture which is daily wasted may, by diet and a right course of moderating ones living, be restored "—The Cure of Old Age—Roger Bacon.

Everyone recognizes that the phenomenon of dehydration must be related to the substances of the body that control the movements of water between tissues. If we are ever to become as optimistic as Bacon and be convinced that the dehydration of age can be reversed, it is probable that we will effect this through our knowledge of composition of some governing constituents, such as sodium chloride. To date the phenomena stand unrelated, but a beginning has been made in studying changes in the composition of the body as senescence approaches.

Other Chemical Changes in the Body

"One of them is fat and grows old, God help the while!"—Henry IV.

In any consideration of the chemical changes in the animal body as the result or cause of the ageing process, two probable sources of error must be kept in mind. In the first place, available data usually cover only the first half of life and we are thus obliged or perhaps tempted to extrapolate into the period of ageing. In the second place, the small amount of available data has been assembled from chemical analyses of lower animals like the rat. Reasoning by analogy we tend to consider these data as applying to man.

An attempt to apply analytical methods to the study of age changes was made by Ehrenberg (112). He analyzed the bodies of mice, the livers, brains and kidneys of rabbits, and the livers and brains of men of different ages. He determined such organic compounds as arginin, histidin, and cystin. He also determined the P and N extracted by alcohol and ether. His data show no real age trends, probably due to variability of individuals and insufficient numbers in the various age groups.

The body fat of the newly born child differs in composition from that of the adult. In early studies, Langer (113) found the fatty acids of the newly born to melt at 51 degrees and those of an adult at 38 degrees. He also found the fat of the child contained butyric and caproic acids which in the adult he could not detect. The differences he found are shown in table 13.

In the early months in the life of a child Jaeckle (114) found the body

TABLE 13

Changes in composition of human body fat with age (113)

	Child	Adult
	%	%
Oleic acid	67.7	89.8
Palmitic acid	29.0	8.2
Stearic acid	3.3	2.0

fat to have a much higher content of fatty acids than in later life. In a newly born child he found the I. No. varied from 39 to 49 while in an adult it had a mean value of 65. This change, however, took place during the first 12 months of life.

His values are the reverse of those of Ssadikow (115). Perhaps modern life in Leningrad and that of a third of a century ago in Pasen account for those differences.

At birth Ssadikow found body fat with an I. No. of 80, while at 35 days of age the value was only 56. A similar value was observed in a 12-year-old cat.

Fehling also found the rabbit embryo of 20 to 30 days of age had 2 to 4.9 per cent fat, while at birth this increased to 6.5 and in the adult averaged 7.8.

Cholesterol as well as fat seems to show age relationships although an ever present possibility continues to haunt the worker, namely, that these sterol changes are specific pathological ones.

The cholesterol and Ca both increase in the aorta of a horse as it grows older. Burger (116) quotes values from the study by Keunhof.

In the lens of cattle eyes the cholesterol also seems to increase with age according to the analyses of Burger and Schlomka (117)

The aortas of 73 cattle of various ages were analyzed for cholesterol and calcium by Gerritzen (118). His values fail to exhibit marked age changes in this species although the regular increase in calcium was marked (table 15).

The skin of man tends to lose both moisture and cholesterol in the process of ageing, although the cholesterol values tend to approach a permanent level after the first few weeks of life. Burger and Schlomka dissected skin

TABLE 14

Cholesterol and calcium in aorta of horse (116)

	Age		
	1-5 years	10-25 years	Over 25 years
Cholesterol (mgm. per cent)	130 5	215	230
Calcium (mgm. per cent)	10 5	20	25

TABLE 15

Cholesterol and calcium in the aortas of cattle (118)

Mean age	Dry matter	Cholesterol		Calcium	
		Fresh	Dry	Fresh	Dry
	per cent	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*
9.5 days	26.6	124 9	482 4	10 3	40 0
30 days	25 9	108.8	401 4	10.1	37.8
2.5 years	26 3	102 3	388.7	11 8	44.8
8 years ..	26 0	101 7	416 5	12 3	48 0
12.5 years	26 1	110.3	431.7	16 6	55 6

from dead patients of various ages. The fluctuations in their analytical values are probably due in part to the complications of pathological changes as well as the preparation of the sample. The cholesterol, dry matter, and nitrogen of the skin at various ages are shown in table 16.

Little attention has been given to the other organic constituents of the body. In the course of other studies Bürger measured the increase of nitrogen in human skin in relation to age. His values probably reflect the changes in water as the skin grows older.

The nitrogen of human skin tends to increase with age.

Bürger also noted the increase in nitrogen in such organs as the lens of the eye.

Iron seems to be deposited in the tissues of old animals. Zondek and

Karp (119) could estimate roughly an animal's age by the iron in such organs as the kidneys. They postulate a definite period in about middle life when the iron shifts from the lower to the higher value. This is summarized in their table for several species.

Thus iron seems to play a role at the end of life as well as a vital part in the early life of a young animal.

Sherman and coworkers (120) have followed the alterations in calcium and phosphorus throughout the life cycle of the rat. The increase in calcium of the body is very rapid during the growth period. This increases from about 0.25 per cent at birth to 1.0 to 1.2 per cent in the bodies of adults. During the period of 280 to 510 days the gain in calcium in the body was very slight. This represents the last half of life in their studies. Females that did not rear young tended to have more body calcium than males,

TABLE 16

Changes in skin composition with age (117)

Age	Cholesterol content, dry basis	Dry matter	N dry basis
	per cent	*per cent*	*per cent*
Fetal and newly born	0.87	25.5	14.1
1 month to 1 year	0.43	30.6	15.0
1–9 years		35.6	15.1
10–29 years	0.34	36.4	16.0
30–49 years	0 28	36.7	15.6
50–69 years	0.27	39.8	15.8
70–89 years	0 29	35 0	15.4

but they did not carry this study beyond middle life to determine if the difference persisted into the period of old age. There was even an increase in the calcium in the body of males from the 8th to the 12th month.

The per cent of calcium in the body of an animal that is retarded in growth tends to exceed the normal, but the total amount is less. Females lose calcium in producing litters, but regain it during the rest period. No data were secured upon these animals during their old age.

AGEING OF THE BLOOD

"Time hath not yet so dried this blood of mine, nor age so eat up my invention."—Much Ado About Nothing.

The blood of animals of different ages has been given more attention by the chemist than any other component of the body. Blood can be studied in the course of ageing because samples can be taken without injury to the individual.

The hemoglobin in the boood of man tends to remain relatively constant after the age of 11 although there is, according to Williamson and Ets (121), some trend toward a decline in the male after the age of 60.

The hemoglobin of rat's blood was measured at twenty day intervals by Williamson and Ets, until their animals were 250 days old. In this species, as in many others, there is a tendency for the hemoglobin to decrease until the young are weaned. After weaning the value increases to a maximum of 15.5 grams per 100 cc. at 5 months of age. After this it tends to remain at about 13.8 gm. until the rat is 250 days old. The latter half of the life span was not studied.

Many studies of the effects of age upon the number of erythrocytes have proved inconclusive. Schwinge (122) reviewed the older literature and concluded the slight changes found in old age were those related to blood concentration rather than total number of cells.

The conflicting evidence concerning the changes in red cells and hemoglobin of the blood has been presented by Millet (123). He also presented some new observations. His data were too variable, however, to be conclusive, but the size of erythrocytes in old age seemed to be definitely larger.

The specific gravity of the blood varies with many physiological factors such as exercise and rest (124). At birth it has a very high value of 1,066 for both sexes. This drops rapidly the first two years and then slowly climbs to a maximum of 1,059 in the male at an age of 35 to 45. After this there is a slow decline to a value of 1,054 at the age of 75. The blood of women tends to have a lower specific gravity than that of men. At the end of life, as at birth, both values are equal.

Bürger (116) finds that there is a progressive lowering of the resistance of erythrocytes to hypotonic solution as a man grows older. He assumes that the blood progressively increases its percentage of old cells as the body ages. These older cells seem to be less resistant.

Blood serum shows an increase in refractive index as an animal grows older. Hatai (125) studied rats from birth until nearly 600 days of age.

The total nitrogen in the blood of rats increases with age (126). At weaning, this value is 0.81 gram per 100 cc. of plasma while at 360 days of age it is 1.22 grams.

Wells (127) followed the change in proteins in rabbits' blood between the ages of 21 and 140 days. The increase was progressive during this period but tended to decrease in adults.

According to Toyama (128), in rats the percentage of total proteins increases rapidly during the suckling period but slowly during puberty. There is little change in the adult, but a slight fall at 385 days. The per cent of albumin increases rapidly for the first thirty days. This falls and then rises again until the end of puberty. The globulin rises steadily u

at 255 days the relative amount of it exceeds the albumin. The per cent of non-protein bodies is quite constant throughout life. The oldest rats used were only 385 days of age, however.

Reiss (129) ran refractive indices upon the blood of children from 1½ days to 18 years of age. He failed to find the progressive changes of Hatai.

As early as 1844 Bacquerel and Rodier claimed the blood cholesterol increased in old age (after Parhon).

From a very limited number of cases Parhon (130) claimed some increase *as a result of age, but his data were few and variable.*

Until rats are about three and a half months of age the blood cholesterol remains below 0.04 per cent. In the adult this may rise to as high as 0.08 per cent according to Roffo (131), although he found no correlation with age. He also determined the total lipids in the blood of rats between the

TABLE 17

Changes in chicken blood with age

(Baker and Carrel (132))

Age	Total lipid	Lipid P	Cholesterol	Protein
	per cent	*mgm*	*mgm*	*per cent*
6 months	0 88	5 7	255*	3.5
4–5 years	1 06	7.4	143	4.6

* Three months.

ages of two and five months. These values varied from 0.3 to 0.6 per cent, but showed no correlation with the age of the animal.

The protein total lipid and lipid phosphorus fractions increase in the blood of ageing chickens, but the cholesterol decreases. The following values were found by Baker and Carrel (132) in the sera of chickens (table 17).

In modern times the cholesterol content of the blood and the forms of cholesterol have been given renewed attention because of the possibility that cholesterol-rich foods might accelerate the development of vascular sclerosis in man as they do in herbivora. Claims have been made that the blood of those subject to atherosclerosis contains large molecules representing combinations of protein and cholesterol (133). Furthermore it has been claimed that foods rich in cholesterol increase these combinations in the blood. It has long been known that the cholesterol of the blood rises and falls in relation to other lipids in the diet (134). Thus a cow kept upon a herbivorous diet containing no cholesterol suffers a decrease of this compound when the lipid content of the diet is decreased. When the diet is increased in these vegetable fats the blood lipids and cholesterol return to normal (135).

In a study of the blood cholesterol in elderly patients, Kountz (136) found that elderly female patients had a higher level than male patients although the onset of atherosclerosis was earlier in the males. Furthermore he found peripheral atherosclerosis more common among patients with low blood cholesterol.

The serum cholesterol in men ranging in age from 18 to 55 years has been determined by Keys (137). No differences were found in different age groups. Furthermore he found no relation between the level of blood cholesterol and the habitual consumption of cholesterol in foods.

Since the animal body is able to make cholesterol and since the level in the blood varies with the other lipids, the problem of relating the cholesterol level of the diet to atherosclerosis is very intricate. Substantial damage to a sound nutrition program in old age may result from attempts to lower the cholesterol in the diet since the foods richest in this substance such as eggs and liver are also excellent sources of vitamins and dietary protein.

The lactic acid seems to rise regularly with the age of man although the regular change may be obscured by such factors as urobilinemia. The values of Loiséleur and Morel (138) show increases of blood lactic acid from 10 to 16 mgm. between the ages of 10 and 60 years.

In old age the mechanisms for handling carbohydrates seem to become less efficient. Marshall (139) ran glucose tolerance tests upon old men. The level of the blood sugar rose to about 22 per cent after the feeding of 50 grams of glucose. This level is higher than that for normal young men. The threshold level also seemed to be higher because glucose did not appear in the urine in most cases unless this threshold level of about 0.2 per cent was exceeded.

Various curves for the decrease of the blood sugar to normal were found. In a fourth of the cases the "log" type of curve was found. A "diabetic" type occurred in half the cases although the men were usually normal.

The gradual failure of the kidneys in the aged is reflected in the higher level of indoxyl and urea in the blood as well as the slower rate of excretion of such substances as phenolsulphonphthalein, according to Laroche and others (140).

The uric acid in the blood of 37 individuals varying in age from 71 to 91 years was determined by Currado (141).

Values ranged from 2.56 to 4.36 mgm. per cent.

The changes in the calcium and various forms of blood phosphorus have been studied in both children and adults by Stearns and Warweg (142). Unfortunately their studies did not include adults in the last half of life but their curves suggest a constancy or rather a wide individual variability after the first few months of childhood. This does not preclude the possi-

bility of variability in these compounds in old age but suggests they are relatively constant in the adult.

Up to the age of 85 the plasma calcium and the plasma lipids fall within the range characteristic of adult men according to the studies of Page and coworkers (143).

In rats Watcham (144) finds the calcium and magnesium of the serum tend to be quite constant throughout life. Young males, however, of 3 to 4 months have a higher magnesium level in their serum than older ones. This averages 5.4 mgm. per 100 cc., while the value for the others of both sexes averages 4.4 mgm. per 100 cc.

Serum calcium tends to be significantly higher in young rats. No seasonal variations were found for either age or sex.

The serum calcium is more variable in the female rat, while in man the reverse is true according to Boynton and Greisheimer (145) as well as Okey, Stewart and Greenwood (146).

In the studies of Greisheimer and others (147) the calcium of the blood sera of both men and women tended to decrease with age. In normal men this fell from a mean of 11.6 mgm. per 100 cc. to one of 10.0 as age progressed. In women the fall was from 11.8 to 9.7. These authors compiled a table summarizing similar data of earlier workers. These data indicated similar changes of about the same magnitude. These findings contrast with those of Page.

The calcium, magnesium and potassium content of muscle and blood of guinea pigs, rabbits, dogs and cats were determined by Cahane (148). His data indicate that the calcium of both muscles and blood changes. In man limited evidence indicates the ratio of K/Ca in the blood of people over 60 tends to be higher.

The sodium of the blood does not change with age. Ornstein and Vascauteano (149) found about the same values at all ages and in both sexes.

The exchange of components between the blood and spinal fluid is not affected by age in the case of man (Katzenelbogen (150)).

Changes in the Composition of Teeth and Bones with Age

"A fair face will wither; a full eye will wax hollow."—Henry V

Much human misery is due to the failure of the bones in later life. Much of the suffering from broken hips is probably preventable if enough study is given to the dietary factors responsible for the maintenance of strong bones in old age. Some study has been given to the inorganic constituents in bone during the past century. However the organic matrix which is equally or more important has been given little attention. Today workers are slowly awakening to the importance of the bone proteins and other organic constituents.

In one of the early textbooks of biochemistry Berzelius (151) included a section comparing the composition of the teeth of men of different ages. He even included data upon the teeth of an Egyptian mummy. His table showed the carbonates to have fallen from about 10 to one per cent in the case of an old man, while the calcium phosphate remained about the same. This table also shows more organic matter and less ash in the teeth of a day old baby than in those of an adult.

In modern times Wilton (152) found the changes in the teeth of guinea pigs suffering from scurvy to be similar to those of old age except the former were reversible.

Wilton also believes the bone changes in scurvy and in ageing to be similar except senile changes proceed much further.

Among the early workers von Bibra (153) devoted much attention to the changes in the composition of bone with age. He compared the composition of the bones of both men and animals. In birds he noted the increase of ash with age. His tables are also interesting because many analyses were run upon individual bones of the body. In regard to age changes von Bibra states, "Hohes Alter selbst ist gewissermassen ein pathologischer Zustand, und ich habe in der That gefunden, dass die Knochen der meisten Greise etwas erweiterte Markkanalchen, mehr Fett und Zugleich etwas weniger anorganische Substanz zeigen, als Knochen, als Knochen von Individuen des Mittleren Alters." The great variability of the ash in human bones prevented von Bibra from drawing definite conclusions. However, he recognized that the ash increased in the bone after birth. His studies included such diverse species as the ox and fox. Thus he sets an example of work in the field of comparative biochemistry that has been used too little in the intervening century.

Even in the time of von Bibra there was considerable literature dealing with the composition of bone. The interest in bone was probably due to the concept that these structures were more resistant to change than the organs of the body and hence represented more certain reflections of the conditions that accompany ageing. The exchange of the constituents of bone is probably more rapid than has generally been realized. Thus Krogh (154) found that after a single dose of radioactive phosphorus given to an adult rat, 29 per cent of this appeared in the bones in a week. Part of it also appeared in the teeth. In young, growing rats relatively more was taken up and the exchange was more rapid.

In advanced age it is known that the fat of the bone marrow is replaced by a semi liquid, gray and translucent material, "gelatinous marrow". The bone marrow is said to comprise 3.4 to 5.9 per cent of the human body, although these values seem high (155). About half of the marrow is red and half fat. In other words, the red marrow equals the liver in weight.

Glikin (156) found lecithin to be very rich in bone marrow at the time of birth. It then drops to a minimum in old age. Glikin extracted bones with ethyl alcohol on the water bath. The bone was ground and the powder extracted in a soxhlet with chloroform. Phosphorus was determined upon this extract. He ran determinations upon the bone marrow of sheep, cattle, horses, swine, as well as upon human beings.

Bolle (157) studied the age variations more extensively than Glikin. He came to the same conclusion, that the phospholipids were high in the marrow of the young in comparison to the old.

In a cat, one half year old, he found over 6 per cent of the bone fat was P-lipid, while in cats 1 to 5 years of age the values were 1.27 to 2.05 per cent.

Little attention has been paid to bone fats, although Reichart (158) found that disease tended to alter the quality as well as the amount of these lipids. Thus he observed a melting point of 43°C. for healthy bone fat and 33°C. for that in certain diseases.

However Newlin found that the lipids of bones represent a mobile store of fats that reflect the diet of the animal both in quality and quantity (159). Hence marrow fats reflect the type of diet and condition of the body rather than changes with age.

Weiske (160) found the feathers and bones of birds exhibited marked changes with age.

Mason (161) could find no increase of ash with age in human bones nor could he confirm Fremy's view that the increase of organic matter with age was responsible for the fragility.

Wildt (162) studied the composition of the bones of rabbits from birth to over 3 years of age.

Wildt felt there was little change in adult bone in the course of ageing.

Aeby (163) studied human as well as animal bones to determine age changes. Between the ages of 19 and 86 he could find no relation between composition and age.

Lehman found the organic substance of different bones to vary. Thus in a forty-year-old suicide he found in humerus 31.5, radius 33.8, ulna 33.2, femur 28.6, fibula 34.1, tibia 34.1. Von Bibra (153) noted various bones of both man and rabbit differed in organic matter.

They also noted different bones of the same body to vary by about six per cent in calcium phosphate.

Individual bones within the body of an animal seem to vary in their ability to maintain their composition, according to the findings of Aron and Sebauer (164) in a dog fed a calcium-poor diet and one fed a normal diet.

This raises the question concerning relative changes in different bones of the body in the course of ageing but no data are available.

In the rib bones and aorta of man the calcium seems to increase with age at about the same rate according to Bürger and Schlomka (117).

These same authors found the dry matter in human rib bones to rise from a value of 20 per cent in newly born to 42 per cent in sixty-five year old people (Bürger and Schlomka (165)).

The rate of growth of an animal may exert some influence upon the composition of the adult bones. Aron (166) noted, however, in the case of dogs retarded in growth, that the bones continued to grow and maintain their composition.

The bones of rats tend to increase in calcium, phosphorus and carbonate as the rat matures according to the studies of Kramer and Shear (167). The proportion of calcium carbonate to the phosphate becomes greater as the rat grows older.

The increase in carbonate has also been observed in the bones of cattle by Neal (168).

The ratio between the calcium phosphate and carbonate tends to decrease in value as the animal matures. In their studies with dairy cattle Neal and coworkers obtained the ratios of 7.3 for animals 6–12 months of age and 6.6 for adults.

In the course of growth, magnesium is deposited in bones at a different rate from the calcium and phosphorus, according to Hammett (169).

The fate of these elements in the course of old age is unknown. Magnesium is especially interesting because of the consumption of this element by some individuals in France in the hopes of retarding senility.

In considering bone ash in the rat Hammett (170) finds a tendency toward a fixed composition in the male at 65 days and in the female at 100 days.

In growing animals bones increase in ash and organic matter with age. Individual bones progress at slightly different rates in these changes. Hammett's data (171) also show the ability of the female to build ash into her bones more rapidly. Hammett did not continue his studies into the latter half of the animal's life.

In the body of the rat about 99 per cent of the calcium is in the bones.

If the percentage composition of the ash is considered, the magnesium is found to decrease in the period from 50 to 65 days of age. This change in the bones of females is about two weeks later than that of males and tends to parallel the water changes. In the ash the per cent of Ca rises and that of P falls as the rat grows from 23 to 150 days.

In rats restricted to a diet low in magnesium, the bone tends to become

unusually heavy and richer in ash, Ca and P, according to Orent and others (172). Unfortunately these studies were only made upon rats up to 55 days of age. The part played by Mg in very old bone remains unknown. The rapid mobilization of Mg when there is a deficiency in the blood of young rats, found by Orent and coworkers, suggests useful experiments for the modification of the bone composition in old animals. In one case of an animal upon a magnesium deficient diet the Mg dropped to a value below 0.1 per cent of the dried bone.

In guinea pigs Tribot (173) found the bones attained their greatest ash content at 150 days of age and then gradually decreased to 555 days after which they remained constant.

From rather extensive studies of Chen (174) it is doubtful if the breaking strength changes much in the course of ageing of rats within the normal span of life. However Chen's data indicate one outstanding biological variable, namely that the femurs become more dense and have a greater breaking strength in females if they are forced through a series of gestation periods without lactation. In her studies performed upon the rats of Bogart and others (175), also Babcock and coworkers (176), the female rats were bred frequently but the young were always killed at birth.

The teeth of a rat lose water and gain in ash continually from 23 to 150 days of age, according to Matsuda. These changes were not followed during old age.

In older research there was a tendency to analyze bones and teeth without regard to the environment or the food of animals. Modern work indicates that these changes in composition reflect the living regime of a given species and that the composition of the bones is subject to profound modification as aging advances.

A start has been made in answering one of the commonest of human questions, namely if the diet of an animal throughout life affects the composition of the bones and teeth when the animal dies in old age.

Modern research using radioactive calcium and phosphorus indicates that the bones, and to a lesser extent the dentine of the teeth, undergo a never ending turnover of inorganic constituents. Furthermore different bones have varied rates of exchange of substances such as calcium. If an old animal is fed radioactive calcium and radioautographs are made of various bones, there is unmistakable evidence that the vertebrae have acquired more of the calcium than the long bones such as the humerus.

Many attempts have been made to answer the question concerning the effects of different diets during the growing period upon the ultimate composition of bones during old age. It is commonly assumed but unproved that the best bones are produced by keeping them calcified to the maximum during the growing period. Kellerman (177) found in the case of rats

that short intermittent fasts during growth, produced bones in the adult that were calcified as well as in the case of animals fed regularly.

In case of very rapid growth of rats upon diets relatively rich in protein but modest in calcium, the calcium content of the bones tends to be lower as the rats attain adult size. No studies have been made of such rats in later life to determine if the bones make good the deficiency during adult life when calcium needs are low (178). However, in earlier work, Kao concluded that higher protein levels led to accelerated growth but no differences in span of life or ability to rear young (179).

No differences were found among three groups of rats reared upon different but high levels of calcium and then kept during adult life upon lower but adequate levels judged by human standards (180).

For nearly a quarter of a century various students in the laboratory at

TABLE 18

Diet and bone density at end of life (rats)

(Unpublished data from Cornell)

Liquid	Bone density		Bone Ca (mgm./ml.)	
	Male	Female	Male	Female
Sugar soln.	1.29	1.36	298	314
Coffee	1.29	1.37	298	313
Water	1.25	1.35	291	312
Milk	1.31	1.38	309	324

Cornell have attempted to discover diets that would produce animals in old age with superior bones and teeth. Most of the earlier studies resulted in failure but recent attempts have been more promising. In unpublished experiments comparing various sources of liquid in the diet of the rat, evidence has been found that diets composed solely of fresh milk supplemented with four trace elements, namely iron, iodine, manganese and copper, produce rats with much better teeth and somewhat superior bones in old age. Some of the data from these studies are summarized (tables 18 and 19).

All rats except the "milk" group were fed an adequate stock diet rich in bone meal and vitamin D. No decayed tooth was found in a rat kept exclusively upon fresh milk. The trend toward superior bone is slight but evident in the rats fed milk although their diet was much lower in calcium than the control groups. Both the density and calcium per unit bone volume were slightly better. These data indicate that ways may be found for the preservation of better bone and teeth in old age. Furthermore they indicate that the bones of the female are superior to those of the male

spite of the greater age of the female at the time of death. These females had never been allowed to reproduce so this variable was not introduced into these studies (fig. 11).

TABLE 19

Decayed lower molars at end of life (rats)

(Unpublished data from Cornell)

Fluid	No of rats	Decayed teeth per rat	Free from decay
			%
Sugar soln	38	2.6	40
Coffee	34	3.8	18
Water	38	2.4	13
Milk ..	34	0	100

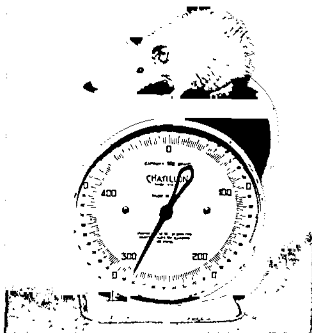


FIG. 11. Ancient female rat that lived its whole life of 920 days (equal 92 years for man) upon a sole diet of fresh, mineralized milk.

TISSUE CULTURE AND THE AGEING OF SERUM

"Old, cold, withered and of intolerable entrails"—Merry Wives of Windsor.

The growth stimulating principles of serum change with the age of the animal. In the early studies of Carrel (181) the superiority of extracts of

the embryo in promoting the growth rate of connective tissue in vitro, was observed. He found extracts of the organs of old animals were less effective in stimulating growth than those of young ones.

Carrel was unable to get an exact measure of the age of an animal from the rate of tissue growth. However, in comparing the growth rates of heart and liver tissues in plasma taken from chickens 4 months, 2 years and 5 years old, there was more growth in the youngest plasma. This also proved true for the growth of connective tissue in the serum from a kitten one month old in comparison to that from an old cat. The same phenomenon proved true in testing sera from human beings 20 and 45 years old.

In a study of the relative effectiveness of plasma of chickens ranging in age from 6 weeks to 9 years, Carrel and Ebeling (182) found the tissue tended to live longer in younger plasma as well as grow more rapidly. The rate of growth tended to decrease more rapidly than the age increased.

Plasma, according to Carrel and Ebeling (183) seems to contain both a growth promoting and an inhibiting substance. Heating at 65° increases this inhibiting property more in the case of young than in that of old animals due in part to destruction of the growth promoting factor. Even after heating, the inhibiting power of the older serum is the greater. The carbon dioxide precipitate from the serum of a young animal stimulates growth of fibroblasts while that from an old animal has no activating power.

The experiments by Carrel need to be extended by studies with sera of other species and by biochemical isolation of the factors responsible for the reactions he has observed.

Kotsovsky (184) found old tissues tended to retard growth. He fed tadpoles with powder from the hearts of old and young animals.

Little additional biological evidence is available showing the effects of age upon such properties as the nutritive value of tissue. However, it is well known that the tissues of adult animals may store large amounts of vitamins whereas the growing animal may consume these factors and have little reserve. Therefore, such observations as those of Kotsovsky may represent crude measurements of such stored factors.

Certain elements such as aluminum tend to increase in the animal body as it grows old. In the organs of puppies Underhill and Peterman (185) could find only traces of Al, while in dogs ranging from 5 to 15 years in age they found the following amounts:

	Al in milligrams per 100 grams of tissue
Liver	0.74-1.42
Kidney	0 -0.20
Brain	0.22-0.38
Lung	0.42-5 15

One might expect the lungs to accumulate considerable aluminum in the course of breathing dusts of clay.

Such accumulated elements may prove to be the basis for differences observed in biological testing.

Practical Conclusions

"Physicians have therefore almost universally preferred simplicity of diet as satiety is soon produced by one than by many substances."—J. Sinclair, Code of Health and Longevity, 1844.

In this era of inflated values, low purchasing power of older people and heavy taxation, few older people can afford ill health. All must conserve funds and buy wisely. Food is a major budgetary essential.

Much of the wisdom of the centuries has more application today than ever before. When Sinclair drew together the knowledge of the past in order to put it to use about a century ago he summarized some of his most important conclusions as follows:

"1. Breathe pure air. 2. Use a moderate proportion of liquid food. 3. Consume no more solid food than the stomach can easily subdue. 4. Preserve the organs of digestion in good order. 5. Take regular exercise without fatigue. 6. Sleep as many hours only as may be necessary to restore the strength of body and mind. 7. Control the passions and bear with fortitude the disappointments of life."

Sinclair laid great stress on the maintenance of function of the gastro-intestinal tract and the prevention of constipation by means of better diet.

The century that has elapsed since the days of Sinclair has given us a new insight into nutritive values and a surer basis for judging the merits of dietary regime. However this same century has created new hazards in nutrition for people of all ages and especially for older folks. The first of these hazards is the danger of inadequate intakes of vitamins, minerals and protein due to decreased exercise and lowered caloric intakes.

Mechanization has decreased human movement so that the typical older person can live with very little compulsory exercise. Hence his intake of foods in terms of energy usually will amount to only 1500 to 2000 calories or about half the intake of an adult or a large youth. With this lowered intake of food every effort must be made to insure high quality, in terms of essentials because the need for such elements as calcium does not decline in proportion to the need for energy. In fact the requirement for calcium rises in old age and may exceed the amount needed at any other period of life. Likewise the need for vitamins and protein seems just as high in old age as in middle life.

The second great hazard in later life is the temptation to consume foods that provide little beside energy. The two that create the greatest danger are alcohol and sugar. The next two in order of importance are cooking fats and white flour. With the exception of alcohol these substances all

offer the additional temptation of being cheap sources of energy They are not cheap if they lead to years of ill health in later life.

The old person, more than any other, needs to shop for natural foods that are both economical and rich in essentials. Some of these foods are dry skim milk, soy flour, dry brewers' yeast, wheat germ, potatoes and whole wheat flour. The best meats are those rich in vitamins such as heart, kidneys and liver. Eggs are nearly complete and the current fear of them because of their cholesterol content is not justified.

Since the older person may be dependent upon foods ready to eat he should give special attention to basic products such as bread. Bread can be made from excellent formulas containing milk, wheat germ, soy flour and yeast or it can be made very poorly of white flour with few additions What is true for bread is also true for breakfast cereals and sweet baked goods.

The older person can help his own diet by mixing dry skim milk or dry yeast into his foods. He can keep a sugar bowl on his table filled with powdered bone meal and another filled with yeast or wheat germ. These supplements can be eaten at each meal. Milk is probably the best food for later life. Tests with animals have indicated that they can be reared and kept for the whole of life upon no other food than fresh milk. Older as well as younger people can profit by the use of more milk.

Among the plant proteins the best is that from soy beans This can be purchased as flour and used in many foods.

Brewers' yeast is one of the richest natural sources of both protein and water soluble vitamins. It can be taken suspended in water just before meals by those who tend to become overweight. It can be used to lessen the need for insulin by diabetics. It may help prevent constipation. Yeast may cause trouble for those afflicted with gout since it is rich in purines.

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bright. The past century has indicated the way for profitable research. The methods followed by the older biochemists of merely analyzing the bodies of animals of different ages proved sterile. The approach by means of carefully planned experiments in which animals are subjected to a given regime during the whole of life appears very promising. Nutritional variables can thus be studied during the whole of life. Results can be measured by the conventional techniques of the physiologist, the biochemist, the nutritionist, the psychologist, the pathologist and others.

Combined with these nutritional variables must be those concerned with the ways of life such as exercise, sleep, mental disturbance and surrounding physical environment. Such research must be long continued. Studies with

animals must often precede or run parallel with those made on man. The end results are certain.

It is hoped that the future may see much more research made upon older people. Homes for the aged, veterans' hospitals, mental hospitals and prisons all afford opportunity for long continued research in the field of nutrition and gerontology. In most cases the "human guinea pigs" involved in such studies would be delighted because they gain personal attention, they are relieved from boredom and they can make a final contribution in advancing the welfare of mankind.

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7

LONGEVITY IN RETROSPECT AND IN PROSPECT

LOUIS I. DUBLIN

New York

The term life span is loosely used. In the popular mind, it connotes with equal frequency the limit of duration of the individual human life and the average length of life of a group of persons. I shall attempt, in this chapter, to consider broadly the ideas that are behind each of these points of view with regard to human longevity.

LIFE SPAN

The life span, properly conceived, is the limit beyond which human life does not extend even in the most favorable circumstances. When we examine into this limit, we find ourselves almost at once in a sphere of vagueness and conjecture. There is no evidence of some definite age at which all human life must necessarily cease. It is difficult, as a matter of fact, to find a body of authentic data with regard to the length of life of persons in the advanced ages. Until fairly recently, birth registration was practiced in a relatively few countries and even in these such registration was not always complete. And so if we find persons who claim to be 150 and more years old in various semi-civilized and rural populations, we may be neither surprised nor impressed with the reliability of such claims. It is significant that claims for extreme old age are frequent in just such backward places where one would hardly expect great longevity.

On the other hand, in more advanced countries where correct recording of age is possible, it is an extremely rare occurrence to find persons who are more than 100 years old. There are, of course, a few individual instances which are very striking. The most quoted example is that of Christen Jacobsen Drakenberg, the Dane, who was supposedly born on November 18, 1626, and died on October 9, 1772, thus living 146 years. Authentic centenarians do exist, but they are very few in number and they pass out

of the picture rapidly. We are thus led to the conclusion that in current times the century mark is, for all practical purposes, the limit of the human life span.

Despite our lack of authenticated data, there is no reason to believe that the life span of the human race, indefinite as it is, has varied appreciably within historical times. The extraordinary life spans referred to in Genesis are obviously mythical and need not concern us here. For some reason, homo sapiens very rarely has the ability to pass the mark of 100 years of life, a fact which may seem strange to some who have grown accustomed to the incessant boast of our increasing longevity. For these people it becomes necessary to distinguish clearly between two fundamentally different concepts, namely, the life span, which has already been defined, and the mean length of life, which is the average number of years lived by all persons born at a given period. The second of these concepts leads us at once to a brief description of the life table, a most useful statistical tool, by means of which we can follow quantitatively and accurately the effect of the ageing process on a population traced from birth to death.

Life Table

The life table, such as that shown by way of example on page 205, is really a simple document to understand when stripped of its technicalities. The basis of the life table is a series of figures showing the death rates for each age of life (see, for example, column 4 of table 1) as derived from our national mortality reports and census volumes, which contain, respectively, the numbers of deaths and the population classified by age. It is characteristic of the column of death rates in a life table that, once the hazardous first year of life is passed, the figures drop rapidly to a minimum at about age 10. From here on, the figures increase slowly to the fifth decade of life, during which the effects of the ageing process become very noticeable in the death rates. Thereafter the death rates increase rapidly.

The survivorship column of the life table (column 2) is easily derived from the column of death rates. Thus, in our example, we start with 100,000 newly born white male babies who experienced, according to the figure opposite age zero in column 4, a death rate of 48.12 per 1,000. Among these 100,000 babies there were, therefore, 4,812 deaths (column 3) in the first year of life, leaving 95,188 to reach their first birthday. Since the death rate at age one was 4.87 per 1,000 living at that age, among 95,188 persons there were

$$95{,}188 \times \frac{4.87}{1{,}000} = 464$$

deaths. The number living to attain age 2 is thus 95,188 $-$464 = 94,724.

TABLE 1

Life table for white males in the United States, 1939 to 1941

1	2	3	4	5	1	2	3	4	5
Age	Of 100,000 born alive		Rate of mortality per 1,000	Complete expectation of life or mean after-lifetime, average number of years lived after age x per person surviving to exact age x	Age	Of 100,000 born alive		Rate of mortality per 1,000	Complete expectation of life or mean after-lifetime, average number of years lived after age x per person surviving to exact age x
	Number surviving to exact age x	Number dying between ages x and $x+1$	Number dying between ages x and $x+1$ among 1,000 living at age x			Number surviving to exact age x	Number dying between ages x and $x+1$	Number dying between ages x and $x+1$ among 1,000 living at age x	
x	l_x	d_x	$1{,}000\ q_x$	$\mathring{e}_x$	x	l_x	d_x	$1{,}000\ q_x$	$\mathring{e}_x$
0	100,000	4812	48.12	62.81	40	86,880	446	5.13	30.03
1	95,188	464	4.87	64.98	41	86,434	479	5.54	29 18
2	94,724	250	2.65	64.30	42	85,955	515	6 00	28.34
3	94,474	179	1.90	63.46	43	85,440	555	6 50	27.51
4	94,295	145	1.53	62.58	44	84,885	600	7.06	26 69
5	94,150	130	1.38	61.68	45	84,285	646	7.66	25.87
6	94,020	116	1.24	60 76	46	83,639	696	8.33	25 07
7	93,904	108	1.14	59.84	47	82,943	750	9.04	24 27
8	93,796	99	1.06	58.91	48	82,193	806	9.81	23.49
9	93,697	96	1.02	57.97	49	81,387	866	10.64	22.72
10	93,601	93	1.00	57.03	50	80,521	930	11.55	21.96
11	93,508	95	1.01	56.08	51	79,591	997	12.53	21.21
12	93,413	99	1.06	55.14	52	78,594	1069	13.60	20.47
13	93,314	106	1.14	54.20	53	77,525	1145	14.76	19.75
14	93,208	119	1.27	53.26	54	76,380	1224	16.02	19.03
15	93,089	133	1.43	52.33	55	75,156	1305	17.37	18.34
16	92,956	147	1.58	51.40	56	73,851	1390	18.81	17 65
17	92,809	160	1.72	50.48	57	72,461	1473	20.34	16.98
18	92,649	172	1.86	49.57	58	70,988	1558	21.95	16.32
19	92,477	184	1.99	48.66	59	69,430	1643	23.66	15.68
20	92,293	195	2.12	47.76	60	67,787	1727	25.48	15.05
21	92,098	205	2.23	46.86	61	66,060	1813	27.43	14.43
22	91,893	214	2.32	45.96	62	64,247	1896	29.52	13.82
23	91,679	218	2.38	45.07	63	62,351	1981	31.77	13.22
24	91,461	220	2.41	44.17	64	60,370	2065	34.20	12.64
25	91,241	222	2.43	43.28	65	58,305	2148	36.85	12.07
26	91,019	223	2.45	42.38	66	56,157	2232	39.75	11.51
27	90,796	228	2.51	41.48	67	53,925	2315	42.93	10.97
28	90,568	234	2.59	40.59	68	51,610	2396	46.43	10.44
29	90,334	242	2.68	39.69	69	49,214	2475	50.28	9.92
30	90,092	251	2.79	38.80	70	46,739	2549	54.54	9.42
31	89,841	262	2.91	37.90	71	44,190	2618	59.24	8.94
32	89,579	274	3.06	37.01	72	41,572	2678	64.43	8.47
33	89,305	288	3.23	36.12	73	38,894	2728	70.14	8.02
34	89,017	304	3.42	35.24	74	36,166	2762	76.37	7.58
35	88,713	322	3.63	34.36	75	33,404	2777	83.13	7.17
36	88,391	342	3.87	33.48	76	30,627	2769	00.40	6.77
37	88,049	364	4.14	32.61	77	27,858	2735	98.18	6.40
38	87,685	389	4.43	31.74	78	25,123	2675	106.47	6.04
39	87,296	416	4.76	30.88	79	22,448	2588	115.30	5.70

TABLE 1—*Continued*

1	2	3	4	5	1	2	3	4	5
	Of 100,000 born alive		Rate of mortality per 1,000	Complete expectation of life or mean after lifetime, average number of years lived after age x per person surviving to exact age x		Of 10,0000 born alive		Rate of mortality per 1,000	Complete expectation of life or mean after lifetime, average number of years lived after age x per person surviving to exact age x
Age	Number surviving to exact age x	Number dying between ages x and $x+1$	Number dying between ages x and $x+1$ among 1,000 living at age x		Age	Numbr surviving to exact age x	Number dying between ages x and $x+1$	Number dying between ages x and $x+1$ among 1,000 living at age x	
x	l_x	d_x	$1{,}000q_x$	$\mathring{e}_x$	x	l_x	d_x	$1{,}000q_x$	$\mathring{e}_x$
80	19,860	2177	124 71	5 38	100	65	26	389 35	1 96
81	17,383	2341	134 72	5.07	101	39	15	402.05	1 90
82	15,042	2187	145 37	4 78	102	24	10	414.29	1 84
83	12,855	2014	156 68	4 51	103	14	6	425 99	1.78
84	10,841	1828	168 59	4 26	104	8	4	437 12	1.73
85	9,013	1631	181.04	4 02	105	4	2	447.60	1.68
86	7,382	1432	193.95	3.80	106	2	1	457.38	1 64
87	5,950	1233	207.27	3 59	107	1	0	466 40	1 61
88	4,717	1042	220 91	3.40	108	1	1	474 62	1 57
89	3,675	863	231.82	3.22					
90	2,812	700	248 94	3 06					
91	2,112	556	263.22	2.90					
92	1,556	432	277 60	2.76					
93	1,124	328	292.02	2.63					
94	796	244	306 42	2 51					
95	552	177	320 76	2.40					
96	375	126	334 96	2.30					
97	249	87	348.98	2.20					
98	162	59	362.75	2.12					
99	103	38	376 23	2 04					

Source: T N E Greville, "United States Life Tables and Actuarial Tables, 1939–1941," Bureau of the Census, Washington, D. C , 1946, p. 34

This procedure is continued to the end of the life table. It will be noted that in the process of computing the survivorship column, we obtained, incidentally, the third column of the life table, which shows how many, out of the 100,000 born alive, die in each age of life.

Let it be assumed, for the sake of simplicity, that each person lives on the average, one-half year in the age of his death; for example, that each of the 4,812 who died in the first year of life lived, on the average, one-half year;[1] that each of the 464 dying in the second year of life lived $1\frac{1}{2}$ years, etc., to the oldest age shown in the table. Altogether, the 100,000 live born babies lived a total of

$$4{,}812 \times \tfrac{1}{2} + 464 \times 1\tfrac{1}{2} + 250 \times 2\tfrac{1}{2} + 179 \times 3\tfrac{1}{2} + \text{etc.} = 6{,}281{,}188 \text{ years of life.}$$

[1] Actually, this average duration is somewhat less than one-half year because of the very high mortality in the first few days of life.

Each of the 100,000 newly-born babies lived, therefore, 6,281,188 ÷ 100,000, or 62.81 years of life on the average. This figure, 62.81 years, is commonly known as the mean length of life or expectation of life at birth. The expectation of life at any age may be conceived in a like manner. Thus, of the 92,293 persons alive at age 20, 195 died after living one-half year in that age, 205 died $1\frac{1}{2}$ years after attaining age 20, etc. The total number of years lived by the 92,293 in the remainder of their lifetime is thus

$$195 \times \tfrac{1}{2} + 205 \times 1\tfrac{1}{2} + 214 \times 2\tfrac{1}{2} + \text{etc.} = 4{,}407{,}507 \text{ years of life}$$

The expectation of life at age 20 is therefore

$$4{,}407{,}507 \div 92{,}293 = 47.76 \text{ years}$$

It is to be noted that the life table shows what would be the number of survivors to successive ages, what would be the number of deaths at successive ages and what the expectation of life would be *if the death rates at each age remained constant as of the calendar year or period for which it is constructed.* With this understanding, let us examine what the life tables constructed for the past have to tell us.

Historical Retrospect of Longevity

Investigators working with data obtained from inscriptions on Roman tombstones have estimated that the mean length of life in antiquity may have been somewhere between 20 and 30 years, on a level with that of such places as India not so long ago. There is some evidence that in the more healthy places the mean length of life may have been as high as 35 years, but this figure is rather doubtful. From this era we must pass to the middle ages for our next indication of the mean length of life, which was then about 33 years according to estimates from records for the higher classes in England. Much later, in 1693, Halley, a noted English astronomer, published the results of his investigation of mortality in the City of Breslau during the period 1687–1691. Although the life table produced by him can not be accepted as typical of that period, the resulting mean length of life, 33.5 years, does not indicate any marked advance over the crude estimates for antiquity.

An extended series of life tables for Sweden, beginning with 1755 and reaching up to 1940, enables us to follow the progress of longevity in a typically Western country which has taken advantage of modern public health practices. The earliest life table, that for the years 1755–1776, showed a mean length of life of 34.5 years, not far from what Halley found for the City of Breslau. The next life table, reflecting conditions during 1816–1840, had a mean length of life of 41.5 years, an advance of 7 years

over the previous table. Tables constructed for successive decennia beginning with 1861 show a steady progress in expectation of life from 44.6 years to 57.0 years for the period 1911–1920; in the next decade, the 60 year mark was passed with a figure of 61.8 years for the first quinquennium and 62.3 years for the second. A further increase to 65.6 years was experienced in 1936–1940. The course of the the expectation of life in the remaining Scandinavian countries, Holland, and England, has been much the same as that just outlined. For us, in this chapter, a particular interest attaches to the situation in the United States.

The first American life table, known as the Wigglesworth Table, was crudely constructed for a period prior to 1789 from data gathered in several towns in New Hampshire and Massachusetts. The mean length of life was found to be 35.5 years, a figure corresponding to that for Sweden of about the same time. Progress for some time thereafter was slow; according to a life table for Massachusetts in 1850, our longevity had advanced to only 40 years by the middle of the nineteenth century.

Shortly before the turn of the century came what may be called the era of discovery of the basic facts with regard to the control of environment, causation of disease, and that series of practical administrative measures which have since been crystallized in the modern public health movement. As this program developed, the expectation of life at birth responded rapidly and definitely so that each new set of tables showed a corresponding increase in the expectation of life. By 1900, the expectation in the United States had jumped to about 50 years; by 1920, to 56 years; and by 1940, to almost 64 years. Today, it is around 68 years. The rapidly improving longevity witnessed so far during this century presents some characteristics that call for special consideration.

Longevity Considered with Regard to Age

Analysis of available data indicates that the constant gain in longevity which we have noted has been largely concentrated in the earlier years of life. For example, we see, in table 2, that among white males in our country, the expectation of life at birth increased from 48.23 years in 1900–1902 to 65.49 years in 1948, a gain of 17.26 years. At age 40, the corresponding gain was 3.00 years; at higher ages the differences are understandably smaller. Although greater gains in expectation of life are observed among the females, the situation is, fundamentally, much the same.

We are inevitably led to the conclusion that the greater part of the gains in the expectation of life at birth may be attributed to the control of infant mortality, to the practical elimination of certain diseases of childhood and to the curtailment of conditions once considered typical of ado-

TABLE 2

Expectation of life and mortality rate per 1,000 among white males and white females in the United States; 1900 to 1902, 1909 to 1911, 1919 to 1921, 1929 to 1931, 1939 to 1941, 1948 for the decennial ages of life

Sex and calendar period	Age 0	10	20	30	40	50	60	70	80
	Expectation of life, years								
Males									
1900–1902	48.23	50.59	42.19	34.88	27.74	20.76	14.35	9.03	5.10
1909–1911	50.23	51.32	42.71	34.87	27.43	20.39	13.98	8.83	5.00
1919–1921	56.34	54.15	45.60	37.65	29.86	22.22	15.25	9.51	5.47
1929–1931	59.12	54.96	46.02	37.54	29.22	21.51	14.72	9.20	5.26
1939–1941	62.81	57.03	47.76	38.80	30.03	21.96	15.05	9.42	5.38
1948	65.49	58.41	48.97	39.79	30.74	22.44	15.40	9.76	5.45
Females									
1900–1902	51.08	52.15	43.77	36.42	29.17	21.89	15.23	9.59	5.50
1909–1911	53.62	53.57	44.88	36.96	29.26	21.74	14.92	9.38	5.35
1919–1921	58.53	55.17	46.46	38.72	30.94	23.12	15.93	9.94	5.70
1929–1931	62.67	57.65	48.52	39.99	31.52	23.41	16.05	9.98	5.63
1939–1941	67.29	60.85	51.38	42.21	33.25	24.72	17.00	10.50	5.88
1948	71.04	63.46	53.80	44.29	35.00	26.16	18.06	11.17	5.85
	Mortality rate per 1,000								
Males									
1900–1902	133.45	2.74	5.94	7.99	10.60	15.37	28.59	58.94	133.53
1909–1911	123.26	2.38	4.80	6.60	10.22	15.53	30.75	62.14	135.75
1919–1921	80.25	2.11	4.27	5.73	7.50	11.74	24.62	54.63	119.73
1929–1931	62.32	1.47	3.18	4.13	6.79	12.78	26.44	57.96	129.97
1939–1941	48.12	1.00	2.12	2.79	5.13	11.55	25.48	54.54	121.71
1948	33.40	.63	1.72	2.00	4.25	10.78	23.73	53.24	110.74
Females									
1900–1902	110.61	2.46	5.54	7.72	9.31	13.37	25.06	53.60	121.15
1909–1911	102.26	2.06	4.20	6.03	8.03	12.59	25.83	50.67	125.79
1919–1921	63.92	1.79	4.33	6.03	6.76	10.67	21.73	50.23	113.41
1929–1931	49.63	1.13	2.77	3.74	5.22	9.59	20.63	45.66	117.42
1939–1941	37.89	.70	1.45	2.20	3.68	7.62	17.14	42.33	108.19
1948	25.70	.41	.85	1.25	2.70	5.91	13.49	36.68	90.53

Source: Reports from the Bureau of the Census and National Office of Vital Statistics. Mortality rates for 1948 computed in the Statistical Bureau of the Metropolitan Life Insurance Company.

lescence and early maturity. Altogether our progress with the diseases of late maturity and old age has not been of any consequence. To date, we have not been able to extend the life span: We observe savings only at those ages where lives were heretofore unnecessarily shortened by the impact of fortuitous factors like the bacterial diseases, many of which are coming under control. The viewpoint thus established naturally leads us to inquire further. What causes of death are typical in the ageing process and at what ages do they first become noticeable? What are the chances of dying from any of the causes typical of old age? How many years of life may be added, on the average, if it were possible in some way as yet unknown to eliminate any of these causes?

Variation in Causes of Death with Age

Aside from the predominance of the congenital conditions as a cause of death in early infancy, deaths at ages under 40 are largely of infectious or accidental origin. Beginning with age 40, however, the cardiovascular-renal diseases (the cardiovascular-renal diseases include the diseases of the heart and arteries, nephritis, intracranial lesions of vascular origin and other diseases of the circulatory system) typical of the ageing process assume rapidly increasing importance. According to the data shown in table 3, which relate to white persons in the general population, one-third or more of all the deaths in the age group 40 to 49 years arise from the degenerative conditions included within this category. The proportion of deaths from the cardiovascular-renal diseases thereafter mounts until ages 80 years and over when it accounts for two-thirds of all deaths. Cancer (including Hodgkin's disease, leukemia and aleukemia) also first becomes an important item at about age 40. Among females between the ages 40 to 59, this cause takes not far from one-third of all deaths; among males between ages 50 to 69, about one-sixth of all deaths arise from cancer. Accidents, an important factor in mortality during youth and early maturity, are of importance again in old age. Pneumonia and influenza as causes of death present an interesting situation for their toll is greatest at the two extremes of life. At ages under 20, one-tenth of all deaths arise from these diseases; at ages 50 to 59, pneumonia and influenza account for only 2 per cent of all deaths, but at ages 80 to 89, they take more than 4 per cent. Although tuberculosis is a sizable item during ages 20 to 39, taking one-eighth of all deaths among females, it decreases in proportion to the total with advancing age. Diabetes is of particular importance among females past midlife.

With a continuance of mortality conditions prevailing in 1948, more than 55 per cent of all children born will eventually die of some cardiovascular-renal disease (see table 4). The chances of dying from this category of

conditions increase thereafter with advancing age and reach 60 per cent by age 10 for white females and by age 30 for white males. For females, the chances of dying from cancer are greater than for males; at birth, the figures are 16 per cent and 14 per cent respectively. The chances of

TABLE 3

Percentage distribution of deaths from specified diseases or conditions. United States, 1948

Disease or condition	Age group							
	0–19	20–39	40–49	50 59	60–69	70–79	80–89	90–99
White males								
All causes	100.0	100.0	100.0	100.0	100 0	100 0	100 0	100 0
Cardiovascular-renal diseases	2.4	19.2	42.0	52.3	58.2	63 8	68 3	68 1
Cancer*	2.5	8.6	12.7	16 6	17.4	15.4	11.0	6.0
Accidents	14.8	36.1	12.2	6 2	4.3	3 5	4 4	5.9
Pneumonia and influenza	9.2	2.3	2.9	2.4	2.5	3.1	4.3	6.2
Tuberculosis	.9	8.6	7.5	4.8	2.8	1 4	.6	.3
Diabetes mellitus	.1	1.1	1.2	2.0	2.6	2.5	1.5	5
All other causes	70.1	24.1	21.5	15.7	12.2	10 3	9 9	13 0
White females								
All causes	100.0	100.0	100.0	100.0	100.0	100 0	100 0	100.0
Cardiovascular-renal diseases	2.7	19.5	32.4	42.5	53.4	63.9	69 5	68.1
Cancer*	2.6	18.9	32.8	31.5	23.5	15 7	9.7	5.5
Accidents	9.6	10.5	4.6	2.9	2.7	4.0	6.4	8 3
Pneumonia and influenza	10.3	2.9	2.1	1.7	2.0	2.9	4.3	5.8
Tuberculosis	1.5	12.8	4.4	2.1	1.3	.8	.3	.2
Diabetes mellitus	.4	1.6	2.3	5.4	7.4	5.2	2.3	.7
Puerperal state	.4	7.8	.8	†				
All other causes	72 5	26 0	20.6	13.9	9.7	7.5	7.5	11.4

* Includes leukemia, aleukemia and Hodgkin's disease.
† .003.

dying from cancer vary only slightly over the life span. Among males, the chances of eventual death from some accidental cause are greater than among females until age 40 years. Pneumonia and influenza show no partiality between the sexes, the risk of eventual death from this combination of causes being close to 3.5 per cent at all ages. Throughout life the white male has a much greater risk of eventual death from tuberculosis than the white female; even at age 50, the figure for white males is as

high as 2.0 per cent. About 4.0 per cent of all females will eventually die of diabetes; for males the chances are about half those for the females.

The question is often raised as to the increase in the mean length of life which would result from the elimination of any one particular cause of death. The answer is of some importance, for it indicates in a forceful manner the directions in which efforts must be led to achieve the most

TABLE 4

Chances per 1,000 of eventually dying from specified diseases or conditions, United States, 1948

Disease or condition	Age 0	10	20	30	40	50	60
White males							
Cardiovascular-renal diseases	558	583	588	597	607	619	636
Cancer	137	142	143	144	145	146	143
Accidents	69	68	63	55	49	44	41
Pneumonia and influenza	35	32	32	32	32	33	34
Tuberculosis	26	27	27	26	24	20	15
Diabetes mellitus	19	20	20	21	21	21	22
All other causes	156	128	127	125	122	117	109
White females							
Cardiovascular-renal diseases	579	599	602	606	613	625	643
Cancer	158	163	163	164	162	156	141
Accidents	52	51	50	48	48	48	50
Pneumonia and influenza	35	33	33	33	33	33	35
Tuberculosis	13	13	13	11	9	8	7
Diabetes mellitus	40	41	41	41	42	43	42
Puerperal state	3	3	2	1	*		
All other causes.	120	97	96	96	93	87	82

* 0.3.

substantial results in prolonging human life. We find, for example, that if there had been no deaths from the cardiovascular-renal diseases in the general population as constituted in 1948, 9.8 years would have been added to the average length of life for white males and 9.0 years for white females. These figures have only academic interest, however. It is quite impossible to expect the complete elimination of the cardiovascular-renal diseases, for the processes of degeneration are inevitable. On the other hand, the figures do show that we have, in these diseases, the greatest room for increasing the average length of life. If it were possible to eliminate cancer as a cause of death the average white male life would be extended 1.8 years

at birth and the average white female life 2.4 years. Progress in the fight against tuberculosis has already been marked; the average length of life would be extended 0.4 years by its complete eradication. Deaths from accidents have become an important factor in our mortality picture; by their complete elimination, the white male would gain 1.8 years in average length of life at birth, and the white female 0.8 years or close to 10 months. The presence of diabetes as a cause of death curtails the average length of life by 0.2 years and by 0.5 years, respectively, among white males and females.

Prospects in Longevity

One may speculate a bit also on the possibilities of further life extension in the future. We have just seen that in the field of the cardiovascular-renal diseases, cancer and accidents there is an appreciable margin within which human longevity may be extended. These margins for improvement, together with a more intensive application of our present knowledge concerning the communicable diseases of childhood and early adult life, may make it possible to eventually stretch the expectation of life to 75 years. However, our record of what has been accomplished and of where we have so far failed and our knowledge of what may be accomplished by a more widespread appreciation of the available public health facilities indicate that a mean length of life of more than 70 years is possible in the immediate future. According to a forecast for 1975, which was made in connection with estimates of future population of the United States, the mean length of life may then be about 71½ years. This forecast was based upon a study of past records, the best current records in individual states and in other countries, and a consideration of the rate of medical advance. It is quite likely that this estimate of future longevity, like others made before it, may turn out to be too conservative; the figure now offered for 1975 is only about 4 years above what we are experiencing at the mid-century.

The results of the forecast life table for 1975, compared with those of life tables for the general population in 1901 and in 1918, are shown graphically in figure 1. The upper panel portrays strikingly the savings in lives made possible by improvement in mortality. Whereas one-quarter of the children born failed to attain age 25 according to the life table for 1901, the corresponding age by the 1948 life table was almost 60 years; in the forecast life table for 1975 the age is well over 65 years. The ages at which the survivors are reduced by one-half and by three-quarters also show marked advances as mortality improves. Comparing the forecast life table with that for the year 1948, there is observed a gain of over 4 years in expectation of life at birth, of almost 3¼ years at age 20, almost

3 years at age 40, and of one year at age 60. The greater part of the gain is thus at the early ages, where almost the entire span of life lies ahead and where, therefore, there is so much more opportunity to reap the advantages of improvements at all ages.

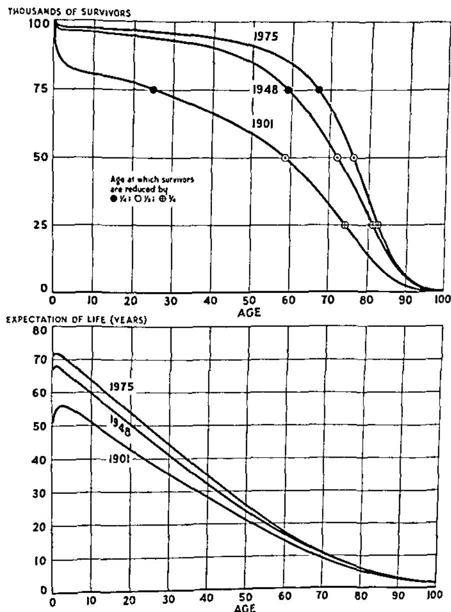


Fig. 1. Comparison of survivorship and expectation of life: life tables for the United States, 1901 to 1948, and forecast for 1975.

Longevity and Population Structure

The consequences of the changing picture of mortality and longevity are many. In this chapter, we need be concerned only with those which flow from the inescapable fact that we are becoming a nation of elders. As more lives are saved from premature death, larger numbers will survive to a ripe old age. This is a fundamental concept that will continue to operate as long as our public health practices move to higher levels. It is brought out in a striking manner by a comparison of the expected survivorship of a cohort of infants on the basis of mortality conditions prevailing in the year of their birth with their actual survivorship in the course of time. To make this comparison, use was made of the life tables for Massachusetts (1). As an example of the results obtained, it was found that, on the one hand, out of 100,000 male infants born in 1890, only 48,700 were expected to survive to age 50 if there had been no improvement in mortality; but when the cohort is traced on the basis of the mortality it actually experienced, then 58,000 survived to age 50. In other words about one-sixth of the males aged 50 years owe their survival to the progress in medicine, public health and general welfare since the year of their birth. For females at age 50, the proportion saved is almost one-fifth.

Another factor of primary importance that has contributed to the ageing of our population is the rapid decline in the birth rate during the period between the two world wars. Although no official nationwide figures exist prior to 1933, it is estimated that the birth rate in the United States in 1910 was approximately 30 per 1,000; by 1925, it had fallen to 25 and since then it declined further to a low point of a little more than 18 per 1,000 in 1933. The following years through 1940 saw the birth rate hover around a level of somewhat less than 20 per 1,000. Although the rate rose sharply during the war period, reaching a maximum of 27 per 1,000 in 1947, it has since declined to 25 per 1,000 in 1949, and may be expected to drop further in the years ahead. Immigration, once a factor of great importance in bringing to this country a large contingent of young people, seems destined to a minor role in our future population picture.

This suggests that we trace briefly the changes in the age composition of the American population since 1850. We see in figure 2 that in 1850 over half, or 52.5 per cent, of the total population was under 20 years of age. At each subsequent census this percentage declined; by 1900 it was 44.4 per cent; today it is somewhat less than 35 per cent. Even more interesting are the figures showing the proportionate increase among those 65 years of age and over during the same period. In 1850, they formed only 2.6 per cent of the total; fifty years later, they formed 4.1 per cent; at the mid-century, the figure rose to 8.2 per cent. In actual number, our

population at ages 65 and over has quadrupled within the first half of this century and it is expected to double again by 1980.

The effects of these changes in the age structure of our population have taken place so gradually that on the whole we have hardly been aware of them. But when we look back little more than a generation, we can see that changes have come; and when we project present trends into the future we cannot avoid the conclusion that these changes will loom large in the life of the individual and of the community of which he is a part.

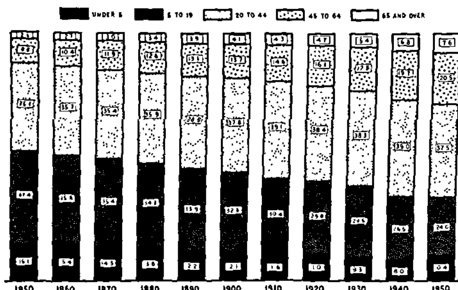


FIG. 2. Percentage distribution of total population by age, United States, 1850 to 1950.

Although it is impossible to trace all the sequences propagated by the increasing importance of the aged in our population, mention may be made of some of the effects upon the economic and social aspects of the nation. Obviously, the burden of dependency upon the productive population will be weighted with an increasing proportion of aged and a decreasing proportion of children. The economic needs of the aged will also take an increasing share of the nation's production. This will be reflected, most directly, in a rapidly rising demand for medical supplies, hospital facilities and practitioners in the medical and allied professions. Even now there is a great need for housing and recreational facilities for the aged; in coming years this will present a special problem—social as well as economic.

The financial problems of the aged—different in our urban economy

from our early rural days—have been receiving added attention from the nation. The start made with our Social Security Act of 1935 was augmented, in 1950, with legislation that increased the numbers made eligible for a monthly income on their retirement and also raised the benefits. Several states—notably New York—have special committees that are devoting particular attention to all aspects of the problems of the aged. Among the most important on their list is that of the work capacity of the aged. At the usual retirement ages, from 65 to 70 years, many still have specialized skills that, where opportunity exists, can add to the productivity of the nation.

Perhaps the most important single effect of such changes in our population structure as we have discussed will be in the mental outlook of the nation. Conservatism may become much more characteristic of our thinking than it is today. The ever-growing number of older people will play a larger part in determining the policy of the country. With a greater proportion of accumulated wisdom in the nation, there will perhaps be a stronger tendency to curtail waste, to utilize the natural resources for the public good and to guide more intelligently the channels of production and distribution. Another accompaniment of the change in population structure is the disturbance in the sex ratio. A larger part of the older survivors will be women, since female mortality in adult life, and especially at the older ages, is considerably lower than that among males.

Whether there will be more or fewer annual deaths in the future than there are now will depend, to a large extent, on the total numbers of our population and on the trend of our death rates, besides the age structure of our population. It is inevitable, however, that, with an increasing concentration of population in the older ages of life where the death rates are highest and even with a continued reduction in mortality at those ages, our country will experience a greater death rate per head of total population than that with which it is now favored. Conditions of morbidity and mortality associated with old age will continue to rise in frequency, relative to the total population. This will be the case with the cardiovascular-renal diseases, cancer, diabetes and certain types of accidents. [illegible] ly experienced [illegible] the other de- [illegible] be attributed to the shift in the age distribution of the population within the last half-century.

Under the regime of an ageing population, the conditions of morbidity and mortality typical of old age may receive the attention to which they have long been entitled but have not always received. Closer study will probably be given to the part played by the infectious diseases in hasten-

ing the degenerative processes associated with old age. Recently acquired knowledge of the relations that exist between endocrine disorders and the ageing process is now regarded as only the initial development in a field of research that promises much. Inheritance of longevity will perhaps be studied more intensively; search will be made for other factors that may affect the ageing process.

An environment which concentrates on the problems of old age cannot help but affect the individual. As his social and economic relations shift, he may be expected to show greater interest in his own prospects for longevity. The possibilities for postponing old age and for mitigating its effects have always found willing ears; the audience will grow more attentive. Individual differences in longevity will be noted more carefully and discussed in the light of the various factors bearing on the chances of attaining a ripe old age.

Longevity and the Individual[2]

There are many factors that bear upon an individual's prospects for a long life. One that will probably remain outside human control is the heritage of longevity bequeathed by the family, for studies that have been conducted on the subject indicate that this characteristic is a hereditary trait. However, gains in average longevity since the beginning of the century have been greater than the differences observed between the best and poorest classifications by parental longevity. The average individual can, therefore, more than overcome biological discrimination by personal and collective action toward the intelligent control of environment, although he cannot altogether avoid the consequences of the qualities that are born with him.

It is now fairly well established that a direct relation exists between social-economic status and mortality. The prospects for a long life are best in the most favored classes and poorest in the unskilled laboring classes. However, there is evidence that the gap between them is closing. This is the result of many factors, in addition to advances in medical science and public health. These other factors are reflected in our better work and home environment and, more generally, in our standard of living. Nevertheless, many industrial workers are still exposed to a wide variety of specific occupational hazards which tend to shorten their lives.

The average length of life has also been found to vary with geographic locality. Those individuals who live in the Prairie States of the Midwest have, on the average, the best longevity in the country, while those who live in the Mountain and Southern States have relatively shorter longevity.

[2] The subject of this discussion is treated in detail in *Length of Life—A study of the Life Table*, (1); see particularly chapters 4, 6, 8 and 11.

However, these variations in longevity may be influenced by occupational characteristics of the different areas. The States with the most favorable longevity are predominantly agricultural, while those with average experience are essentially industrial. Another factor to be considered in this connection is the variation in public health activities within the country. An important factor in the relatively unfavorable record of the Mountain States is the presence of a large segment of Spanish-speaking population on a low standard of living with poor sanitary facilities. Thus, the individual's *chances for a long life are affected by the locality he lives in*, besides the work he does.

There is now an abundance of evidence to show that the married generally experience lower death rates than either the single, widowed or divorced. The exception is found among young married women who are exposed, in large numbers, to the risks of childbirth. Such differentials in mortality by marital status may be expected, for marriage is essentially a selective process into which only the more physically fit enter. That it also confers benefits of various kinds, which directly or indirectly are conducive to longer life, can hardly be questioned.

An individual's personal history of physical or mental ailments has a very significant bearing upon his prospects for a long life. Insurance investigations have shown that a history of certain impairments is often associated with mortality in excess of normal. Many of the illnesses to which the individual falls a victim during the course of his lifetime leave indelible marks that affect his longevity. Abnormalities of build, such as marked overweight, also involve some degree of curtailment in longevity.

The factors indicated in the preceding paragraphs are obviously but a few of the more important items which affect the length of life of the individual. Perhaps more important than any of these factors are the steps that the individual may take on his own behalf to correct or control the hardships of his environment. Evidence of value is accumulating that through the practice of better personal hygiene, by correct and adequate nutrition, and by means of a well ordered existence, the average man may add many years to his expectation of life. The possibilities along these lines have never been fully explored. Recent demonstrations in the science of nutrition have produced striking evidence of what the individual may do for himself in this direction. There are also many instances of greatly improved physical condition and of enhanced longevity through the practice of personal hygiene. Furthermore, when light is shed on some of the many unsolved problems of geriatrics, it may be that the individual will have, within his reach, additional means for a fuller and longer life. In any case, the individual certainly can take advantage of current medical skill to a greater degree than in the past, not only during periods of illness

but also to forestall serious developments through periodic health examinations. The individual may also take steps on his own behalf to improve the conditions in his work and home environment. However, in taking these steps, he is benefited from the collective efforts made in the past to promote human longevity. They indicate clearly what may be accomplished when this practice becomes more general among large numbers of individuals.

Summary

By some inexorable law, still to be discovered and clarified, nature has allotted to man a life span of about 100 years. But very few lives complete this span. Some are so malformed at the beginning of their existence that they cannot continue to live; others inherit limitations on account of constitutional weaknesses. The great majority of newly created lives, which are prepared to live through an existence that terminates only by physical degeneration, are constantly exposed to adverse influences in their environment that threaten either to destroy their existence or to accelerate the degenerative processes. It is within the powers of man, with his natural gift for controlling the forces of his environment, to mitigate or remove these adverse influences. The individual may accomplish much for himself in this direction by accommodating his routine so as to follow sound rules of diet and personal hygiene and by showing an intelligent interest in current public health activities. Acting collectively with his fellow-men either through governmental or private bodies, he has at his disposal vast resources that may be used to meet and overcome difficulties affecting the public health. By such individual and collective efforts, it should be possible to extend the average length of life to a maximum of about 75 years.

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Section II

CHAPTERS 8 TO 36

CLINICAL AND ORGANIC PROBLEMS OF AGEING

8

AGEING IN THE NERVOUS SYSTEM

JAMES L. O'LEARY

St Louis

It is my good fortune that the several scientists principally responsible for my early training live today and continue to inspire my efforts through correspondence. Though each suffers from one or another infirmity of age all remain keen of wit and intellectually productive and have continued to grow in wisdom through the years. Thus ageing is not entirely determined chronologically; the changes are not uniform in all systems, nor does ageing progress to the same degree in the different structures of one system. Certain men and women in the later decades of life may retain good memories and possess keen intelligence, even though their skeletal system or other areas exhibit evidence of profound regressive alterations.

The usual gross examination of the senile human brain reveals changes to be described briefly as a prelude to the section to follow. The meninges are thickened, sometimes adherent and difficult to detach from the underlying cortex, and the Pacchionian granulations hypertrophied. Patchy calcification may occur in the meninges over the convexity and in the falx. The cerebrum often reveals a generalized atrophy, and the lateral ventricles are increased in size. The color of the gray matter may be deeper than that of the brain of a younger adult.

Histology of Ageing

There is evidence that loss of neurones (stated to be a principal concomitant of ageing in old age) occurs even during the growth and differen-

I am indebted to Dr. K. Schwremberg of the University of Michigan School of Medicine for permission to study the excellent Hortega preparations from which the photomicrographs of figure 1 were obtained, and to Dr. R. L. Lam who took them. I am also indebted to Dr. J. L. Fetterman, Cleveland, Ohio, who contributed ideas and read the manuscript critically. Dr. A. B. Jones, St Louis, Mo. also aided me.

tiation of the nervous system in the embryonic period. That more neuroblasts develop than survive is hinted in the writings of Ramon y Cajal and recently Hamburger and Levi-Montalcini (16) have made an important experimental contribution on this subject. They found degenerating cells in the spinal ganglia and in the lateral motor horn of the cervical region of the spinal cord in chick embryos and studied the phenomenon in detail in the spinal ganglia. The peak of cytolysis was found to occur at five to six days, and degenerating cells had practically disappeared at the end of the seventh day. Such large scale degeneration of differentiating cells occurred in cervical and thoracic ganglia but was practically absent in brachial (limb-innervating) ganglia. The degenerating cells were localized in the ventrolateral sectors of the ganglia, parts which previously had contained the large, early differentiating neuroblasts. Experimentally overloaded ganglia (limb bud grafts) showed an increase in the number of early differentiating neurones which might amount to 80 per cent; limb extirpation resulted in a rapid degeneration and disappearance of numerous neuroblasts in limb ganglia where that process does not occur normally.

That cellular alteration is a prime factor in ageing of the brain was shown by Andrew (2) who studied ageing of nerve cells extensively both in man and in the experimental animal. In the mouse Andrew (3) found that both ageing and inanition produced similar appearances in pyramidal cells of the cerebral cortex. Many cell outlines became shrunken and irregular. (The cytoplasm came to appear hypochromatic with little or no Nissl material evident, and the nuclei became basophilic. He saw definite evidence of glial proliferation and active neuronophagia.) The cerebral cortex in two starved senile mice showed cell degeneration, gliosis and neuronophagia which was more evident than in control senile mice. The normally coarsely granular Golgi apparatus of senile pyramidal cells was not visibly affected by starvation, whereas in younger mice the net-like Golgi apparatus was stated to separate into minute granules. In another study of 19 mice representing stages from youth to senility Andrew and Andrew (4) reported no consistent differences between cortical cells of fresh and fatigued animals provided that animals of the same age were compared. Andrew and Cardwell (5) observed changes similar to the above in the senile human cortex and believed them to be a natural phenomenon of ageing in man. Andrew (3) also studied the Purkinje cell from birth to senility in 34 human subjects. In brains of subjects over 50 years old he found that a large number of Purkinje cells had scanty Nissl substance in their cytoplasm. The ground substance of the nuclei was likely to stain similarly to the cytoplasm and the nucleoli to be pale. Cell outlines were often irregular.

Histological evidence of ageing in the human brain is best assayed when

a period of senile dementia precedes death and there is minimal evidence of cerebral arteriosclerosis. Adherence to the first criterion provides opportunity for attempting correlations between severity of alterations noted, duration of dementia and chronological age; relative absence of arteriosclerosis insures, in so far as it is possible to do so, that the changes observed are primary and not the result of vascular ageing.

Significant alteration or loss of cortical neurones is one of the most frequently reported changes in the ageing human brain. In Rothschild's (30) series of 24 cases (66 to 100 years at time of death) there were widespread alterations in cortical nerve cells in all cases and a less extensive decrease in their number. The commonest change was in the ill-defined character of the Nissl bodies which in 7 cases appeared as pale stained material scattered through the cytoplasm. As a result alcohol-fixed cortices presented a washed out appearance as compared with controls. Such cell alteration and loss might be expected as an inevitable occurrence in the cerebral cortex when there is a long-standing history of senile dementia. Yet in the cortex of one 107 year old individual with a history of senile dementia for eleven years reported by Riese and Zfass (27) the cytoarchitecture was well preserved, areas of pyramidization, granularization and spindilization being clearly obvious. Processes of repair and regeneration were detectable. In a later study Riese (26) examined the brains of 18 such individuals who died between 77 and 107 years. All but 5 had senile dementia of eleven months to fourteen years' duration. Riese found cell changes to be consistently present but not to occur in proportion to chronological age or duration of dementia. For example, more severe cell degeneration was observed at age 90 with a one year history of dementia than in the 107 year old brain with an eleven year history. Satellitosis was not a constant feature and did not parallel the degree of cell destruction in Riese's study.

Besides the loss of nerve cells in the ageing human brain, characteristic changes occur in the intercellular matrix, the glia, and the intracellular neurofibrils. Figure 1, composed of photomicrographs from sections of a single ageing human brain (female, age 73, history of senile dementia, minimal arteriosclerotic change) stained by different variants of the Hortega method, illustrates some such changes. *A*, from the cornu Ammonis, shows proliferation and hypertrophic changes in astrocytes. *B* is a typical microglial cell with swollen processes from the neighborhood of a senile plaque in the frontal cortex. *C* is a small senile argentophile plaque from the same region containing a similar microglia. *D* is a larger cortical plaque which had no cellular content. *E* and *F* are characteristic of change in the neurofibrillar apparatus (Alzheimer baskets), also observed commonly enough in ageing cortical pyramids.

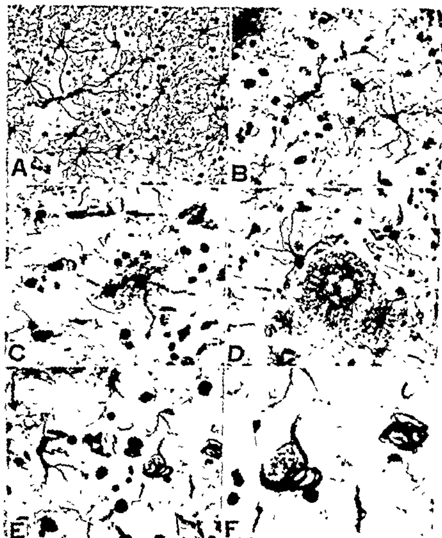


FIG. 1 Characteristic senile changes in the brain of a 73 year old female with diagnosis of senile dementia *A*, field of hypertrophied astrocytes from the cornu Ammonis, × 600 *B*, microglia with swollen processes, frontal cortex, × 600 *B*, microglia with swollen processes, frontal cortex, × 400 *C*, small senile plaque containing microglia, frontal cortex, × 340 *D*, larger plaque with neighboring astrocyte, × 600. *E*, Alzheimer neurofibrillar basket and neighboring microglia with swollen processes, × 660. *F*, another of the same, × 1350. Different variants of the Hortega method were used

Argentophile plaques were first described in the brain of a senile epileptic by Blocq and Marinesco (7). Since then they have come to be considered an outstanding histological manifestation of ageing in the human brain. They occur most numerously in the deeper layers of the cortex of the

frontal lobe and in the cornu Ammonis. A variety of explanations have been made to account for them Simchowicz (35) suspected that the plaques arise by atrophy in the finest neural elements followed by thickening of the neuroglial reticulum. As the reticular meshes become smaller products of metabolism are deposited and neuroglial cells (microglia, fig. 1, C) start to remove them. Růžička's (32) protoplasmahysteresis has also been invoked to explain them. Marinesco (22) believed that plaques arise out of local metabolic disturbance whereby lipoid substances with affinity for silver are precipitated from the lipo-protein complex of the nervous parenchyma, and after invasion by phagocytic microglial cells often degenerate to form amyloid substance. Löwenberg (20) suggested hypotheses of peculiarity in cortical reticulum favoring plaque formation and of capillary fibrosis. Bouman (8) called attention to coexistence in the same senile brains having plaques of "torpedoes" on the neurites of Purkinje cells, swellings on their dendrites and of knots, eyes and buds in neurites passing through cerebral plaques. He believed that these and the occurrence of the Alzheimer neurofibrillary change in cortical nerve cells (fig. 1, E and F) were evidence of hyperdifferentiation associated with ageing and defined that process as an attempt of the nervous tissues to differentiate in the direction of a specific neurone. Bouman considered hyperdifferentiation in the glial reticulum a possible factor in the origin of plaques, since neurites themselves develop within the protoplasm of the reticulum. Soniat (36) thought that the majority of senile plaques arise from degenerating nerve cells and emphasized the importance of the Alzheimer neurofibrillary change in relation to cell degeneration He supposed that later the necrobiotic residuum may attract microglia. Wertham (41) did not consider that plaques arise in the normal senile involution of the brain but are an expression of metabolic alteration in the widest sense.

(4) Increase in lipoid-containing pigment also occurs. Intracellular lipoid pigment can make its appearance in early life in the cells of certain nerve centers, but in old age the pigment increases in amount and tends to become more dispersed through the cytoplasm. It has also been identified in neuroglial cells, in the walls of vessels and in adventitial spaces.

Finally, it may be said that histologically demonstrable damage must represent the end result of ageing in the nervous system, since usual histological methods are too insensitive to reveal fine changes. Likewise, the parts of the cortex are not totipotent in function; and minimal involvement (even submicroscopic) of some areas might be expected to produce a more significant disruption of behavior than would occur in the case of other areas showing more evident histological change. Thus, for research on ageing of nervous tissue to proceed apace with that of other organs it is imperative that data be acquired by animal experimentation

demonstrating effects upon electrical activity and upon the chemical substrate.

OTHER BIOLOGICAL ASPECTS OF AGEING

There is a dearth of specific knowledge concerning the chemical processes which underlie the functioning of the nerve cell. However, it is fair to presume from information drawn from other sources that enzymatic action plays an important role. Ageing might result from (or be contributed to by) disturbances in enzymatic activity in one of several ways: 1) imbalance developing between several enzymes of a balanced system; 2) certain enzymatic activities becoming progressively degradative; 3) endogenous or exogenous toxins decelerating enzymatic action. Improper nutrition or defective enzymatic activity in liver or kidney might be contributory factors. Fazekas and Alman (13) have recently reviewed (the pathophysiology of cerebral metabolic disease and classify disturbances as due to: changes in substrate supply (hypoglycemia); changes in intracellular enzymatic activity (acceleration, inhibition or lack); and changes in oxygen availability.) They conclude that cerebral metabolism proceeds normally at a maximum rate and although it may be depressed there is no conclusive evidence that normal adult cerebral metabolic rate can be accelerated.

An important experimental contribution by Ward and Wheateley (40) illustrates the way in which lessening or cessation in enzymatic activity *may affect the nerve centers progressively. Following sudden intravenous* injection of NaCN (0.5 to 1.2 mgm. per kgm.) into cats and monkeys these authors found the electrical activity of the central nervous system to be depressed from above downward in the order of cortex, basal ganglia, hypothalamus and midbrain. Moderate or no depression of activity was seen in portions of the pons and medulla surveyed, and cord activity might be somewhat increased. They believed symptomatology in their animals could be explained by blocking of enzymatic cell metabolism.

Faulty detoxication as a factor in psychological manifestations of ageing

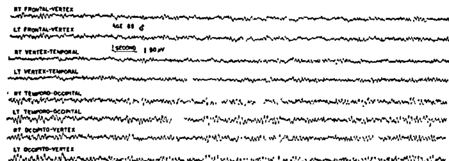
hippuric acid test. The entire group was split between those having involutional psychoses and senile psychoses. Evidence of faulty detoxication was present in more than 3 times the number of persons 60 years of age and older than had been found by previous investigators of mentally normal people belonging to the same age group. However, a small number of senile dementia patients had low values even when compared with patients of the same age suffering from affective disorders or from hypertensive encephalopathy.

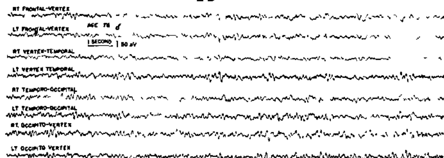
The electroencephalogram is a direct index of brain activity, and the usual basic resting frequency may show definite slowing in the later decades of life. In part this may result from the effect of diminished cellular metabolism upon the usual alpha rhythm. Gibbs and Gibbs (14) illustrated such slow EEGs and their observations have been confirmed since by other workers. Examples from aged people without neurological deficit are shown in figure 2, *A* and *B*. How the EEG contributes to the diagnosis of focal cortical and subcortical lesions in the senile group is made evident in the next section.

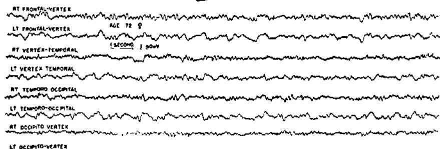
An interesting study of the serological response of Japanese old people to Japanese B encephalitis mouse brain vaccine (ID 50 of 0.013 cc.; Sabin, Ginder, Matu and Schlesinger, 33) illustrates another aspect of the ageing process. Of 7 old people without antibodies before inoculation with mouse brain vaccine none developed neutralizing or complement-fixing antibodies. Ten old people who had neutralizing antibodies before inoculation all developed complement-fixing antibodies in response to the inoculations. In contrast, of 10 children none of whom had antibodies before vaccination, all developed antibodies (also ID 50 of 0.013 cc.).

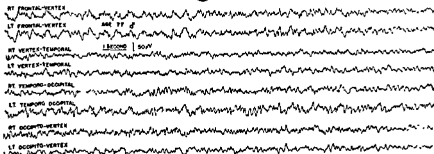
Neurological Aspects

The norms for neurological evaluation of ageing subjects differ from those for average adults in several respects. As ageing progresses the individual becomes less adept at fine movements. Habitude may be characterized by semiflexion at the principal joints, resistance to passive movement and slowness of willed activities, giving the impression that significant involvement of the basal ganglia exists. However, a general outfall of neurones may lead in age to a predominance of the flexor musculature, and the infirmities of joints and tendons also contribute to the change in posture. The same musculo-skeletal infirmities may contribute to the shortening of stride and unsteady gait which lead eventually to a shuffling, propulsive wide-based walk. The musculature may be hypertonic and the knee jerk overactive during normal ageing; ankle jerks may be much reduced, but are rarely absent unless that finding has clinical significance. Again, vibratory sensibility is often diminished so significantly in the distal parts of the extremities (particularly the legs) of old people that this test loses some of its value in detecting evidence of posterior column involvement such as occurs in combined sclerosis. When it is only reduced or perverted (as, for example, being experienced as hot or cold) in the very old, the observation has debatable significance. Even so completely absent vibratory sensibility has significance. Small pupils and slowness of pupillary response amounting to sluggishness may be due to atrophic change in the iridial musculature.


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Certain neurological symptoms are encountered commonly enough in ageing patients. Among these are syncopal attacks and vertigo Less frequent, and usually associated with significant organic cerebral pathology, are senile tremor, Parkinson syndrome, chorea and convulsions According to Engel (12), "When repeated fainting begins after middle life, organic disease of the heart, cerebral blood vessels, and vagus and sympathetic reflex pathways are the most likely causes." True vertigo has been described, particularly by Holmes (17) and Dandy (11), as sometimes occurring through impingement by arteriosclerotic vessels on the eighth cranial nerve. If an attack of severe vertigo occurs in old age, partial or complete occlusion of the long circumflex arteries of the brain stem, particularly anterior inferior and posterior inferior cerebellars, either independently or incident to disease of the basilar trunk, should always be considered in the differential diagnosis.

Critchley (9) believes that senile tremor, occurring apart from essential heredofamilial tremor which may appear at any stage of life, is an uncommon physical finding in old age. Heredofamilial tremor, according to Critchley, may resemble that of either cerebellar or pallido-striatal disease and thus bears a possible remote relationship with Parkinson's disease and with presenile cerebellar atrophies. Cases of outspoken Parkinson's syndrome with tremor at rest may also develop in the aged and be due to selective cell decay or to arteriosclerotic changes in the basal ganglia. Choreiform movements, appearing diffusely, or in an arm, or as hemichorea, or combined with hemiballistic and athetoid components, can occur suddenly in old age and are usually attributed to minor hemorrhages in the strio-subthalamic system associated with arteriosclerosis. In certain cases there is a sudden appearance of choreiform movements which apparently relates to a marked emotional disturbance such as might be occasioned by the death of a near relative, then it is difficult to ascertain whether the symptom is the result of a coincident vascular alteration or due to the unveiling of a dyskinesia which had remained latent previously in spite of progressive focal vascular impairment.

Convulsions making their first appearance in the senium are likely to arise from cerebral disorder which develops incident to arteriosclerosis. The seizures may be generalized or of focal, motor or sensory, Jacksonian character. In rare instances relatively continuous partial motor seizures involve a terminal part such as the face unilaterally; when such occurs

[illegible]

subsequently removed.

changes, gliosis of the white matter and degeneration in the inferior olivary nucleus. All were interpreted as parenchymatous degeneration with subsequent glial reaction.

Whereas the fascinating manifestations of premature ageing of especially vulnerable fiber systems and the intricate overlappings between different so-called clinical entities emphasize strongly the genetic factors which operate in determining cell susceptibility, they continue to have a speculative role in explaining CNS changes in old age. The most cogent recent argument for further investigation of genetically determined factors in ageing has been put forth by Roth (29), who concludes, "It is possible, therefore, that the prospect has been opened up by the concepts of modern genetics and neuropathology, of an attack upon important aspects of the problem of ageing via the degenerative disorders of the nervous system, and of a deeper insight into the latter by further investigation of the phenomenon of senility with a combination of clinico-pathological and genetic studies."

Psychiatric Aspects

Psychological manifestations of ageing bear an inseparable relation to neurological changes and likewise necessitate a knowledge of the principal features of normal senility if one is to recognize the symptoms of the senile psychoses. Granick (15), surveying the results of intelligence testing, found the following trends in the psychology of senility. In subjects over 40 there is a marked progressive decline in overall test performance as related to increasing age. However, where speed of response is not a factor older adults achieve as well as younger ones. Memory functioning, efficiency of performance and tasks involving the relinquishing of old habits are found to be difficult for old people. However, Granick emphasized that healthy old adults are capable of making significant contributions to cultural, industrial and social institutions.

Observations during normal ageing indicate a progressive restriction in forming new interests, reduction in new learning and decrease in aggression and physical performance. Nevertheless, any general lessening in alertness may be more than compensated for by the prudent weighing that has been gained from past experience. With increasing age the individual survives his life-long intimates. Thus interpersonal contacts become progressively impoverished, and free social relationships are not established readily with younger replacements. Conceptual thinking becomes progressively simplified; anecdotes from past experience are called upon with increasing frequency to illustrate present situations. (Discussing anecdotalism in a different context, Schnierla (34) has noted that it is "chronically subjective and not experimental in tendency.") If nominal aphasia develops it also becomes difficult to express concepts, and in the effort required

the particular linkage between past and present is too quickly lost sight of. There is an increasingly *poorer memory for recent events, and talk about* the past replaces that about current incidents. The temporary joy occasioned by the visit of a son or daughter or past intimate is not followed by the keenness of their absence when they depart. The fine edge of judgment may be dulled, as in the individual whose harsh appraisal of competitors in his earlier life now turns towards the wife whom he had previously treated with the warmest affection in all circumstances.

Physiological ageing of the mind may be accelerated by extraneous factors. The loss of a near relative, financial insecurity, dulling of sensory acuity (as hearing) or even being told by a physician that the blood pressure has risen are examples of accelerators. The rise of a younger employee at work may excite persecutory trends as the importance, security and irreplaceability of the aged individual is threatened. Thus it is understandable that the ageing person protects his own interests by not recognizing his decreasing capacities and instead blames others for taking unfair advantage.

Rothschild (31), a foremost authority upon the psychiatric aspects of ageing, recently surveyed the differences between senile and arteriosclerotic psychoses, although recognizing of course that admixtures occur. He points out that psychoses of both classes are preceded by the gradual diminution of physical and mental capacity consistent with normal old age. In both conditions exaggeration of prior personality traits may occasionally be noted as an early feature; as intellectual failure occurs there is loss of efficiency, impairment of memory, errors of judgment, sleeplessness and restlessness. However, the underlying pathological processes are dissimilar and Rothschild believes that the clinical manifestations differ in important respects. Arteriosclerotics often have headache, dizziness, syncopal episodes, convulsive seizures, symptoms of cardiac decompensation or apoplectiform attacks. They may complain of weakness, of fatigue and of a variety of unpleasant somatic feelings. Emotional instability is not uncommon among them. Whereas arteriosclerotic psychoses may develop slowly, as is usually the case with the senile, the course is often stormy, manifestations making their appearance precipitously and being aggravated episodically. (An experienced clinician remarked that the course of cerebral arteriosclerosis proceeds by fits and starts, while that of senile dementia progresses smoothly.) Besides the slow development of the senile psychoses there is usually absence of symptoms suggesting focal damage to the brain and symptomatology divides into simple, depressed and agitated, delirious and confused, presbyophrenic and paranoid types. There is a greater frequency of senile psychoses among women and of arteriosclerotic psychoses among men.

√Regardless of whether senile change is primary or is contributed to by coincident arteriosclerotic involvement, an important factor would appear to be the lessening in or deviation from the proper metabolism of the congeries of cells arranged in *hierarchies of increasing complexity upon* which the mental life depends. We may assume that much is determined *by enzyme-substrate relationships which are subject to a variety of interferences.* The experimental study of Ward and Wheatcley (40) previously *referred to is an example of how blocking of enzymatic cell metabolism* might occur and have differential effects upon the cell hierarchies of the [illegible] to the process of age- [illegible] normal senium can be understood and differences in rate of progress reconciled.

SUMMARY

Several aspects of ageing of the nervous system are reviewed with the *conclusion that the same factors operate in different individuals in varying* degrees.

That certain biologically superior individuals can extend the productive spans of their careers far into the senium suggests that genetically deter*mined factors play an important role in establishing resistance to neuronal,* vascular and glial ageing, all of which must contribute to the neural and *psychic manifestations of senility.*

As a part of the ordered differentiation of the nervous system certain neuroblasts undergo decay after a brief span of development. This suggests that cellular loss in the nervous system can be a general component of overall biological design, though ordinarily it is held in abeyance from fetal life to the onset of the senium. Certain families display hereditary patterns of neurological deficit due to premature cellular decay in particularly vulnerable fiber systems, and there is sufficient overlapping between several such conditions to suggest that in some familial instances at least a single gene acted upon by different modifiers may be responsible. The classical form of presenile dementia, Alzheimer's disease, also has familial examples, and histologically the manifestations of ageing there are very similar to those observed in senile brains.

In addition to the obvious and important effects of vascular ageing, it is likely that metabolic and toxic factors also operate. The senile plaque, characteristic histological finding in the ageing brain, is often used as an illustration of metabolic alteration. If toxic effects are broadened to include the repercussions on the nervous system of faulty metabolism in liver and kidney, it is logical to assume that they, too, may play an important role in ageing of the nervous system.

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9

THE EYE

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The complex anatomical structure of the eye and its adnexa includes within its small extent examples of almost all the tissue types found in the rest of the body. In addition, the eye contains avascular structures—the cornea, lens and vitreous that are not duplicated elsewhere. The number and variety of senile changes to be found in this small organ is, therefore, very great. The older literature with its emphasis on the morphological aspects of senescence is very abundant in regard to the eye. The Surgeon-General's catalog lists five monographs on this subject published between 1895 and 1905. More modern studies concerning the chemical and physico-chemical senescent changes in the ocular tissues are less extensive. An excellent view of these latter studies is to be found in the book by Krause (21). More recently Rones (24) reviewed the subject with special emphasis on the morphological pathology of degenerative changes in aged eyes. A general review by Rutherford (26) on gerontology and the eye should also be mentioned.

The interpretation of changes commonly found in the ocular tissues of the aged is fraught with the same difficulties that have been confronted in every chapter of this book. Are these changes brought about by the unavoidable processes inherent in the mere existence of these tissues over a prolonged period of time, are these changes in the ocular tissues produced indirectly by the senescence or disease of other perhaps remote organs; are they produced by the prolonged and cumulative effects of subliminal insults inflicted by the imperfect environment in which we live, or finally, are they the evidence of disease processes which happen to occur most frequently in the aged but which are, themselves, not directly related to the passage of time? These questions are, for the most part, unanswerable on the basis of the present data and may, indeed,

be essentially unanswerable. For the purposes of the present discussion, changes which occur commonly or universally in the aged will be regarded as senescent changes. Changes which are, themselves, of infrequent incidence but which occur exclusively or almost exclusively in the aged will be regarded as diseases unless they can clearly be shown to represent merely an exaggerated and extreme form of some more usual senile change. It must be admitted that we are here assuming that the senescent process is not strictly dependent upon the calendar age and, furthermore, that the degree of senescence of a particular organ or tissue is not strictly dependent upon the degree of senescence of the body as a whole. Such assumptions are, however, implicit in any attempt to study the process of ageing in individual organs, since without these assumptions the only relevant data would be the calendar age and final length of life of the individual.

Life Span

Total loss of function of the eye, i.e., blindness, may be taken as equivalent to death of the organ. It should be possible, therefore, to compute by methods similar to those illustrated by Dublin in Chapter 8 the life span and average life expectancy of this organ. Such computations for the organism as a whole are based on the age specific mortality rates. To make an equivalent computation with regard to the duration of vision one would require a knowledge of the number of people annually becoming blind in each age group. Such data are not directly available at present, though it is to be hoped that statistics which will necessarily be collected in connection with the blind pension service will some day be available for this analysis. The best that can be done at the present time is to take the census data as to the proportion of blind in each age group of the population. This is probably an underestimate of the true amount of blindness, first because the census probably represents an under count in this respect, and second, because the average length of life of the blind is probably somewhat less than that of the rest of the population. Figure 1 presents the data gathered in the 1910 census. Since only 2.5 per cent of persons over 85 years of age are blind, it is necessary to plot the curves logarithmically in order that survival of vision and survival of life should appear on the same chart.

The two curves have many points of similarity. There is an initial rapid fall corresponding to the high infantile death rate and the high incidence of congenital and juvenile blindness. This fall is almost completed at age 2 years in the life table diagram but reaches a corresponding point only at 12 years in the sight diagram. Following this there is a gently sloping plateau that extends through the fifteenth year for life, the twenty-fifth year for sight. Following this plateau both curves fall at a

slowly increasing rate. At extreme old age the life table diagram flattens out. This final segment of the curve is not represented in the sight diagram, but it is plain that the number of survivors with vision could not reach zero at an age younger than 120 or 130 years.

Though the vast majority of persons live their whole lives without becoming blind, it is not to be assumed that their visual efficiency remains unimpaired with advancing age. The relation of visual acuity to age was first studied by Donders (6). Several others writers (Boerma and

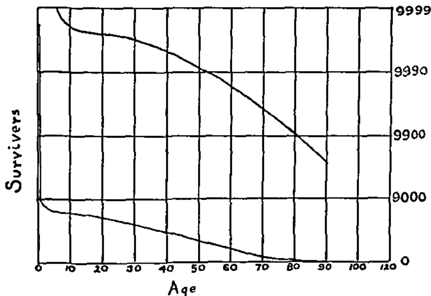


FIG. 1. The lower curve shows the survivors at each age of a group of 10,000 simultaneously conceived. The upper curve shows the survivors with vision in the same group assuming that none died. Based on data of U. S Census 1910.

Walther (3); Boussuge (4)) have at various times made similar analyses on groups of old people. The results of a few of these investigators are shown in *figure 2*. In some of these studies the effort was made to exclude "disease" from the statistical group. The marked differences between the findings of the different observers may be due in part to a different definition as to what is disease and in part to actual differences in the population studied It is to be noted, however, that all these investigators agree in finding a steady fall in visual acuity as age progresses.

It has been shown that the extent of the visual field is less in the aged (Ferree and Rand (7)); that the speed of dark adaptation is decreased and the minimal threshold of light perception raised (Ferree and Rand (8)); that aged eyes suffer a greater proportionate loss of visual acuity

in dim illumination; and it is probable that the critical speed of flicker is also reduced in the aged (Ferree and Rand (9). These studies have not, however, been sufficiently extensive to make possible a statistical analysis as to the average age of onset and average rate of progress of the decline of these functions. It is nevertheless clear that in respect of all *the measurable visual functions the eyes of otherwise healthy old persons* are slightly less efficient than those of the young. The characteristic

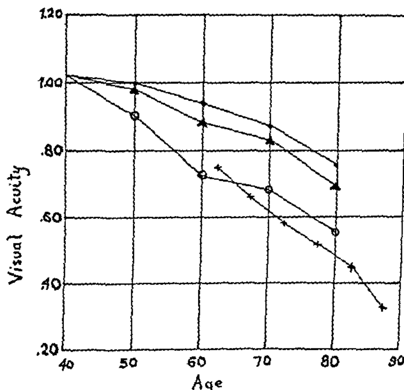


Fig. 2. Relation of visual acuity to age

changes in refraction and reduction of the amplitude of accommodation with age will be discussed below.

Ocular Diseases of the Aged

Aside from changes in the eye directly resulting from sclerotic changes in the local blood vessels, there are several diseases which are responsible for so large a share of the blindness of the aged that their relation to the senescent process requires some discussion. The most important of these are cataract and glaucoma.

The lens is, histologically, such a simple structure that its possible

response to injury is limited almost exclusively to cataract formation. It is no wonder, therefore, that a multiplicity of possible causes of this condition have been discovered. However, if we set aside those instances of cataract which are clearly due to injury, metabolic disease, congenital defect, etc., and consider only idiopathic forms of the disease we are confronted with a phenomenon clearly related to advancing years In spite of numerous efforts it has not, as yet, been possible to discover in exactly what way the senescent process causes this local manifestation. A certain degree of hereditary predisposition is clear for cataracts frequently appear in the eyes of siblings at nearly the same age. While most patients with cataracts show obvious evidence of general arteriosclerosis, it is by no means established that the degree of arteriosclerosis of patients with cataracts is in general in excess of that found in other persons of the same age. Nevertheless, the possibility remains that sclerotic changes in the vessels upon which the lens depends for its nutrition may be excessive in cases of cataract. Attempts to correlate senile cataract with some disturbance in the blood chemistry have been unavailing. It has been argued by some that the cumulative effect of many years' exposure to sunlight, especially if that light contains an undue amount of ultra violet, may be responsible for the trouble—and it is pointed out in this connection that cataract is much more frequent in India than in the western world. In this country, however, the states of Colorado and Wyoming, which stand near the top of the list for intensity of the ultra violet component of sunlight, stand near the bottom in the incidence of cataract. Current studies on the possible relation of vitamin defect to the etiology of cataract have not exhausted the field but, as yet, contributed nothing of significance to our understanding of senile cataract. Salit has called attention to the fact that patients in the Dust Bowl area present themselves for operation at the clinics in higher frequency in seasons following severe droughts. Whether this is the result of economic, nutritional or direct climatic influences is not clear.

It may be pointed out that the lens is dependent for its nutrition upon the capillaries of the ciliary processes and that with advancing age the interstitial tissue surrounding these capillaries becomes denser and frequently shows hyalin degeneration (Kerschbaumer (19)). In addition, the capsule of the lens becomes thicker, denser and less permeable with age (Friedenwald (10)). The possible influence of these phenomena on the metabolism of the lens is obvious, but it has not been shown that these changes occur in excessive degree in cases which develop cataracts.

The diseases of which increased intraocular pressure is the chief symptom are multifarious, but if cases due to congenital malformation and cases secondary to injury or inflammation of the eye are excluded and

only primary glaucoma is considered we are confronted with a disease whose incidence is almost exclusively in the age period beyond middle life. The disease occurs in two forms: acute congestive and chronic non-congestive glaucoma.

Acute congestive glaucoma has been shown to result from a vasomotor crisis in the ciliary body with congestion of the capillaries in the ciliary processes and serous and fibrinous extravasations from these vessels. No explanation is available as to why this should occur more frequently in persons of advancing years. Indeed, similar vasomotor disturbances in other organs appear to be more common in the younger age groups. There is no evidence of excessive local or general arteriosclerosis in these cases, nor is this disease associated with arteriolar sclerosis and malignant hypertension. It must be pointed out that acute congestive glaucoma occurs most commonly between 45 and 65 whereas the non-congestive forms of this disease have a somewhat later age incidence.

Chronic non-congestive glaucoma apparently results from a decreasing efficiency of the mechanism normally responsible for the reabsorption of the intraocular fluid. Sclerosis and hyalin degeneration of the tissues surrounding Schlemm's canal are commonly seen in the advanced stages of this disease but are generally absent at its onset. It has been suggested that the outflow channels may be plugged by granules of melanin pigment which, as we shall see below, are discharged into the anterior chamber from the ageing iris, but this has not been confirmed by histological study of cases examined in the early stages of the disease. There is no evidence that the degree of general arteriosclerosis is excessive in cases of glaucoma, but the possibility remains that excessive arteriosclerosis of the local vessels may be important, and indeed some evidence in favor of this hypothesis has been advanced (Friedenwald (11)). Kronfeld (22, 23) finds that in cases of this type the canal of Schlemm does not become as rapidly nor as completely filled with blood after anterior chamber puncture as it does in normal eyes.

Senile Changes in Ocular Tissues

Orbit and ocular adnexa

A diminution of orbital fat leading to enophthalmus is responsible for one of the most characteristic physiognomic features of senescence. No evidence has been brought forward indicating a weakening of the extra-ocular muscles in the aged, but the amplitude of convergence is generally less in old individuals, and there is often an increasing degree of exophoria. A slight drooping of the upper lid is very common, but this appears to be due to a lengthening of the tendon of the levator muscle rather than to weakness of the muscle. The eyelids of the aged are thin, lacking in

subcutaneous fat and show a marked loss of elasticity. If the lids of a young person are pulled away from the eye and then suddenly released they snap back into place often with an audible click. In the aged they sink more slowly into place and often do not return to their normal position without the intervention of muscular contraction. In extreme degrees of this condition the lower lid hangs permanently away from the eyeball and becomes everted. This progressive loss of tone in the lids usually begins in the sixth decade of life. There is no loss of function in the lachrymal gland attributable to age, but histological examination reveals an increase in the interstitial fibrous tissue of this organ in the aged.

Conjunctiva

The conjunctiva is exposed to numerous and repeated traumata throughout life. This is especially true in persons whose occupations or habits of life include much exposure to the wind and weather. We may, therefore, roughly assume that those afflictions, such as pterygium, which occur commonly in aged persons of outdoor occupations are due to the effects of trauma, while those that occur with equal frequency in persons who lead a sheltered life are, for the purposes of this discussion considered as senile manifestations The conjunctiva of the aged is thin and friable. Hyalinization of the sub-epithelial connective tissue is common. There is frequently a dilatation of the conjunctival veins. Calcareous concretions in the serous glands of the palpebral conjunctiva is very common. One of the most striking differences between the conjunctiva of the aged and the young is the loss of lymphoid tissue, and more particularly the loss of the propensity of this tissue to hypertrophy (follicular conjunctivitis) under the influence of mild irritants.

Cornea

The cornea tends to lose somewhat of its luster and transparency with advancing age. The former is attributable to the accumulation of minor irregularities in the epithelial surface. The latter is poorly understood, since we have no adequate explanation of the transparency of the tissue in the young. The corneal fibers tend to become slightly thicker with age and the water content of the tissue is somewhat reduced. According to Bürger and Schlomka (5) the water content of bovine corneal tissue decreases from 85.4 per cent at age 7 days to 81.3 per cent at age 14.1 years.

In almost all elderly persons and in a few young individuals a ring of opacification develops close to the corneal margin. An interesting statistical study on the age incidence of the corneal arcus has been published by Hinnen (17). Histological examination reveals a lipoid infil-

tration—cholesterol esters and neutral fats—in the affected tissue. The clinically visible arcus is, however, only a small part of the lipoid infiltration of the ocular tissues in these cases. Bowman's and Descemet's membranes in the cornea are even more intensely infiltrated than the corneal stroma. Lipoid infiltration of the sclera goes hand in hand with the arcus. Perivascular lipoidal changes in the iris, subepithelial lipoid infiltration in the ciliary body, and lipoid infiltration of Bruch's membrane are all part of the same symptom complex. The relation of these phenomena to senescence is not clear. Experimentally the whole com-

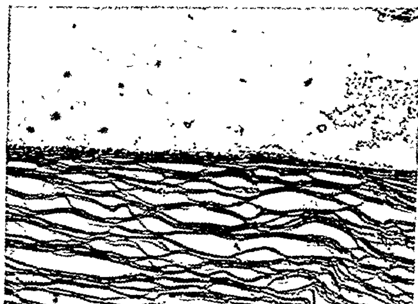


FIG. 3. Henle warts in Descemet's Membrane. Patient aged 70

plex can be reproduced in rabbits by feeding large doses of cholesterol (Versé (32)) and is accompanied in these animals by the deposition of atheromatous plaques in the arteries. Current opinion is inclined, therefore, to attribute both the ocular lipoid infiltration and the atheromatous plaques to some disturbance of the lipoid metabolism. Instances of juvenile arcus can, at times, be accounted for on the basis of hypercholesterolemia due to biliary obstruction or nephrosis, but the cholsterolemia of hypothyroidism does not appear to be associated with these lesions.

In addition to the lipoid infiltrations, local globular thickenings of Descemet's membrane are seen with great regularity in the aged. These were first described by Henle and are known as Henle warts (fig. 3). They are generally limited to the periphery of the cornea but occasionally cover the whole posterior surface of the cornea like dew drops, and may

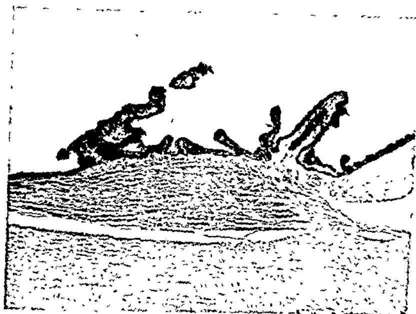
then cause slight decrease in visual acuity. In a small proportion of individuals in whom this widespread distribution of Henle warts occurs, there develops a change in corneal permeability with resultant chronic edema of the cornea and the formation of blisters on the corneal surface (epithelial dystrophy of the cornea)—a condition which leads eventually to blindness. A shallow circular groove at the corneal margin is seen in the aged, presumably due to an atrophy of the tissues in this region

Iris

The color of the eyes fades in the aged. The pupil is small and reacts feebly. The histological basis for these changes has been carefully studied by Fuchs (13) and Seefelder (28). The collagen fibers of the iris, especially in its anterior layers, become denser and thus cast a veil over the deeper lying pigment. Along with this the complex pattern of crypts and trabeculae on the iris surface becomes flattened out and obscured. Similar increase in the collagen fibers about the blood vessels, often with hyalin degeneration, is found. The sphincter pupillae undergoes fibrosis and hyalinization. A peculiar feature which occurs very regularly after the sixth decade (Hinnen (17)) is a loss of pigment from the pigment epithelium on the posterior surface of the iris This begins in small spots at the pupillary margin which subsequently grow and coalesce giving the iris finally a moth eaten appearance. Much of the pigment is discharged into the anterior chamber and can be seen deposited on the posterior surface of the cornea and on the trabeculae at the filtration angle. The pattern of the pigment atrophy does not correspond to the anatomical units in the iris vascular supply and is, therefore, not readily attributable to local arteriosclerosis. Except for the loss of pigment the epithelial cells appear quite normal.

Ciliary body

The histological changes in the ciliary body with advancing age have been described exhaustively by Kirschbaumer (19), Herbert (16) and Fuchs (15). The increasing fibrosis, lipoid infiltration and hyalinization of the ciliary processes with advancing age have already been noted. The ciliary muscle likewise shows an increase in its interstitial fibrous tissue and the muscle fibers in the aged are thinner and denser than in the young (fig. 4). There is, however, no marked decrease in muscular power, as has been shown by very detailed studies of van der Hoeve and Fheringa (31). They have made it quite clear that the declining range of accommodation is to be attributed to changes in the lens, not in the ciliary muscle.



A



B

FIG. 4. Age changes in the ciliary body

Lens

The lens is an epithelial structure surrounded by a homogeneous glassy capsule. No blood vessels enter the lens and its metabolic exchange is,

therefore, dependent upon the nutritive characteristics of the surrounding aqueous fluid and the permeability of the lens capsule. Throughout life new lens fibers are continuously being proliferated by the growth and elongation of the epithelial cells at the lens equator. New fibers are laid down on top of older ones, and the life history of the lens fiber can be studied by observing the differences between successive layers of fibers. Those at the center of the lens were produced during the early months of intrauterine life, those at the periphery are embryonal even in an aged individual.

These cells begin their differentiation as flat hexagonal epithelium; gradually elongating, they assume the form of a tall thin fiber still hexagonal in cross section. The length of individual fibers composed of a single cell attains at a maximum several millimeters. The cell or fiber during its

TABLE 1

Relation of the amount of protein to the age of the lens

From Jess (18)

Age of lens	Weight of lens	Total protein	Soluble protein
	gm.	*per cent*	*per cent*
5 weeks	0.9309	32.33	24.95
1.5 years	1.8522	34.5	19.93
4 years	2 0508	34 24	19.41
6 years	2.5416	36.0	17 62
12 years	2.6720	35 59	17.69
16 years	2.6788	35 5	16.10

period of growth is surrounded by a membrane containing lipoid. The cytoplasm is a homogeneous material of very high protein content. During the period of growth the nucleus remains apparently unchanged but with cessation of growth of the fiber, the nucleus disappears. Subsequently the cell membrane also disappears and the cytoplasm, losing water, becomes dense, rigid, almost horny in character. Chemically these changes are characterized by an increase in the amount of insoluble protein, phospholipids and cholesterol, and calcium, and a relative increase of sodium as compared to potassium, together with an loss of water and of glutathione (nitroprusside reaction).

It is apparent that one cannot speak unambiguously of an aged lens, for the lens contains from birth to old age parts which are embryonal in character and parts which are old. The difference between an old and a young lens is, therefore, a difference in the relative proportion of young and old tissue within it, and senescence for the lens represents essentially the accumulation of a larger and larger proportion of inert desiccated tissue in its center. While the lens grows continuously throughout life the

growth rate is not constant but becomes slower and slower as age advances, never reaching zero, however, unless the tissue dies in cataract formation (fig. 5).

Since the young portion near the surface of the lens is soft and deformable while the older portion nearer the center is rigid, the cortex alone takes part in the act of accommodation, and as the cortex occupies progressively a smaller fraction of the whole volume of the lens, the amplitude of accommodative change decreases. *This decrease begins at birth and* proceeds with remarkable uniformity as age progresses (fig. 6). Such dif-

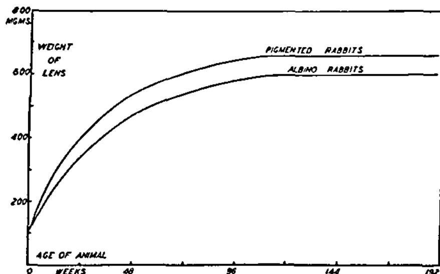


Fig. 5. The weight of the lens of pigmented and albino rabbits at various ages (Krause).

ferences as are found between different individuals of the same age are largely dependent on the different amounts of muscular effort at accommodation which the individuals can be induced to make, for the fluctuations in successive tests on the same individual are nearly as great as the fluctuations between different individuals. Bernstein (1) has studied statistically the variations in accommodative power of different individuals of the same age with variations in their subsequent length of life and has found a positive correlation between accommodative power and longevity. It would be highly desirable to have these studies amplified on a large and more modern body of material. If Bernstein's findings are confirmed, the measurement of accommodative power may attain the position of a useful index of the degree of senescence of the individual. Nevertheless the question will still remain open as to whether the variations measured represent

variations in deformability of the lens or variations in muscular effort of the subject.

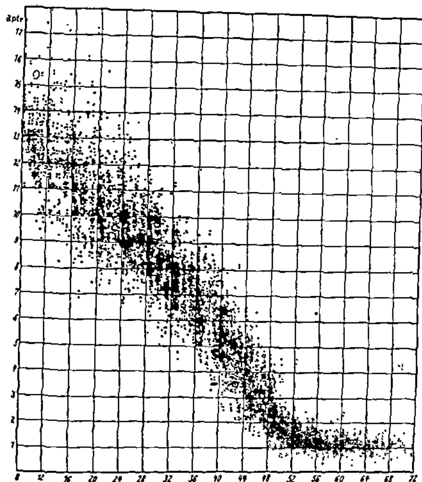


FIG 6 Range of accommodation in 4000 cases (Duane)

Vitreous

The vitreous is an inert non-living tissue. It consists of an insoluble framework arranged in more or less concentric sheets and a mucoid fluid. No change in the fluid has been noted with age but the insoluble framework increases in amount, the sheets becoming more and more closely packed in the periphery. It is apparent, therefore, that we are dealing here again with a process of accumulation of non-vital material. The older

sheets in the central portion of the vitreous tend, as time goes on, to show irregular regions of collapse and agglutination so that an increasing number of floating vitreous opacities is the rule. The increased density and number of the lamellae close to the retina is responsible for one of the most promi-

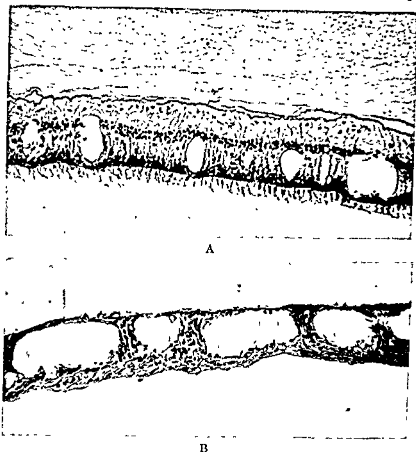


Fig. 7. Beginning and advanced cystic degeneration of the retina

nent ophthalmoscopic changes seen in the aged, namely a dulling of the lustrous sheen of the retinal surface.

Retina

Changes in retinal function with age have already been discussed. In the periphery of the retina near the ciliary body degenerative changes appear quite regularly in otherwise healthy eyes in the fifth decade (fig. 7). When ocular disease is present these changes may appear much earlier. They consist in the disappearance of the middle nuclear layer and its replacement by fluid spaces which on section appear round or oval but

actually form an interlacing pattern of tunnels or channels. The fluid contains a basophilic material which gives the histological reactions of mucin. The distribution of these atrophic changes does not correspond to any anatomical unit of the retinal vascular tree and it is difficult, therefore, to attribute them to local arteriosclerosis. Nevertheless, it must be pointed out the the zone of atrophy is that farthest from the parent arterial supply of the retina, and lesions of this type are not found in dogs—animals notoriously free from arteriosclerosis. As age proceeds the cystic degeneration extends progressively farther back toward the posterior pole but it rarely reaches behind the equator of the eye. It seems reasonable to attribute the progressive narrowing of the visual field in the aged to this change.

The remainder of the retina is thinner and denser in the aged than in the young, apparently due to a loss of water. A variety of senile atrophic and degenerative changes especially in the macular region of the retina should be enumerated among the diseases of the aged, but they all appear to be the consequences of local arteriosclerosis and will not be discussed further.

Choroid

The arteries of the choroid, like those of the spleen, show marked thickening and hyalinization of their media beginning in middle life even in the absence of any evidence of generalized arteriolar sclerosis (Wood, 33). The nature of this change and its relation or lack of relation to the histologically similar changes in the vessels of other organs in cases of malignant hypertension constitute an interesting problem, the solution of which must wait on a better understanding of the pathogenesis of arteriolar sclerosis. In addition to this puzzling phenomenon there is an increase in the interstitial fibrillar tissue of the choroid with advancing years (Kerschbaumer, 20). Bruch's membrane, which lies between the choroid and the pigment epithelium of the retina, becomes thicker with age and partakes of the lipoid infiltration described above in connection with the lipoid arcus of the cornea. This membrane is strikingly similar to Descemet's membrane on the inner surface of the cornea, and like it shows localized nodular thickenings in the aged analogous to the warts of Henle (fig. 8).

Sclera

The sclera of the aged is thinner and denser than that of the young and shows a loss of water. In a recent study Friedenwald (12) has developed a method for the measurement of the distensibility, or its reciprocal, the rigidity, of the eyeball in the living individual. The application of this measurement to otherwise normal eyes of varying ages revealed an increasing ocular rigidity which first appears in the sixth decade of life (fig. 9).

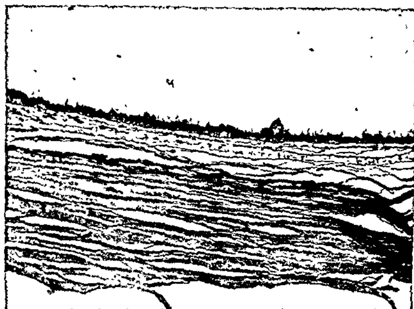


FIG. 8. Nodular thickenings of Bruch's membrane Patient aged 70

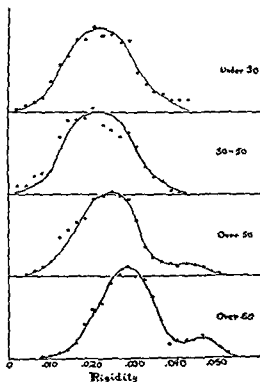


FIG. 9. Frequency distribution of ocular rigidity in different age groups (Friedenwald).

The function which is measured includes not only the elasticity of the sclera but also the pliability of the cornea and the compressibility of the intraocular vascular bed, but the elasticity of the sclera appears to be the most important factor in the measurement. Since the sclera is composed of relatively undifferentiated fibrous tissue the measurement of its elasticity may be useful as an index of the ageing of the connective tissue of the body as a whole. Further studies along these lines are indicated.

Optic nerve

Senile atrophy of the optic nerve is a well established clinical phenomenon but the work of Fuchs (14) has shown very clearly that this is the result of local arteriosclerosis. There is an increase in the interstitial fibrillar tissue (fibrous and glial tissue between the nerve fiber bundles) and an increase in the thickness and density of the trabeculae of the pia-arachnoid of the optic nerve sheath (fig. 10). Basophilic concretions (corpora amylacea) in the meningeal sheath are commonly seen in the aged.

Changes of refraction

In youth the cornea in the vast majority of cases is more curved in its vertical than in its horizontal meridian. The resulting astigmatism is as a rule partially or completely compensated for by a slight tilting of the lens. With advancing age, especially after the fifth decade, this asymmetry of the cornea disappears. Bodenheimer (2) has suggested that the corneal astigmatism of youth results from the pressure of the eyelids on the upper and lower margins of the cornea when the eyes are open. As the tonus in the lids decreases this influence is diminished and the corneal curvature becomes more spherical. At the same time an increase in the tilting of the lens about its vertical axis increases the refractive power of the horizontal meridian of the eyeball as a whole so that astigmatism with the major axis horizontal is the rule in the aged while astigmatism with the major axis vertical is the rule in youth.

With the growth of lens the anterior surface of this organ approaches more closely to the posterior surface of the cornea (fig. 11). Consequently the anterior chamber becomes shallower with age (Rosengren, (25)) and the optical nodal points of the lens move forward. This results in an increase in the effective dioptric power of the lens and hence a slight tendency toward myopia. With the progressive growth and increased density of the lens nucleus, the refractive power of this portion of the lens is increased, adding to the myopic tendency. These two phenomena together account for the short sight of the aged which, if it follows normal presbyopia, often gives the individual a false sense of rejuvenation since he finds himself at an advanced age once more able to read without glasses. The phenomenon

has been referred to as "second sight". Changes in accommodation have been discussed above.



A



B

Fig. 10. Increase in thickness and density of trabeculae of piaarachnoid of optic nerve sheath with age: A—young; B—old.

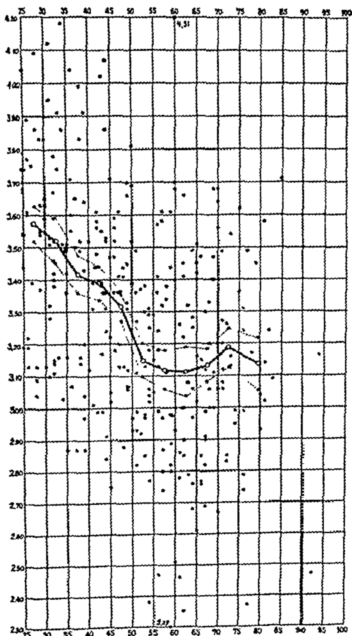


FIG. 11. Depth of anterior chamber in 1000 cases (Rosengren)

Summary

By comparing the expectancy of sight with the expectancy of life it is clearly demonstrable that the normal life span of the eye as a functioning organ exceeds that of the body as a whole. There is, however, a steady decrease of the average efficiency of all measurable visual functions with advancing age even in otherwise healthy eyes. The characteristic senile morphological and chemical changes of the ocular tissues may be summarized as increased density, loss of water, increased interstitial fibrillar tissue, accumulation in some portions of the organ of an increased amount of inert material, loss of fat and of elasticity, together with isolated examples of some rather bizarre forms of tissue atrophy. In relation to the eye, as in relation to other organs, the dominant and at present insoluble problem of senescence is as to whether these changes represent inherent tendencies of mortal flesh, or whether they represent the cumulative effects of potentially avoidable disease or of potentially avoidable subclinical damage produced by a non-ideal environment.

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10

THE EAR

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St. Louis

The present chapter is not a historical account of the attempt to relate high tone hearing loss and advancing age. That such actually occurs, for most individuals, is a well established and long recognized fact. Guild (1) in his chapter on "The Ear" for previous editions of this volume discussed the results of different authors (Bunch (2, 3), Bunch and Raiford (4), Ciocco (5), and others) on the basis of age variations and auditory acuity. Advances in the fields of audiology, clinical otology and laboratory methods justify a discussion of the problems in the light of more recent work. Deafness is no longer measured wholly on the basis of inability to hear certain frequencies. The ability to understand speech under different conditions and the adaptability of a deafened individual to his work, family life and environment are now recognized as extremely important. Various new tests have had to be devised for this purpose. For the aged individual with marked hearing loss the psychological factors such as a feeling of insecurity, fear and the inability to learn new things readily serve to complicate the situation. Attempts at rehabilitation cannot meet with the same degree of success as for younger individuals.

Throughout the older literature are many descriptions of histological changes in the inner ear with old age. For the most part it is not possible to accept these as tenable because many of them have been shown to be artefacts. The human temporal bone is not suitable for a study of cytological details because the delicate endorgans of the cochlea are extremely susceptible to autolytic changes. It is only by newer histochemical methods and immediate fixation of specimens that changes can be adequately evaluated.

A program searching for the causes of high tone loss with ageing can only

be accomplished experimentally with animals of different ages under optimum laboratory conditions

Nothing is known of the effects of age upon the vestibular apparatus. No direct histological or physiological effects have been reported. The reason most frequently offered as an explanation when compared to cochlear function is that the vestibular apparatus is older phylogenetically. Vestibular tests are not particularly refined but considerable progress in perfecting them has been made in recent years. In the future it may be possible to find some correlation. Certainly, any effects of ageing it might reveal could not be as much in evidence as those related to hearing.

Deafness

Prevalence of deafness

There are now available the results of several different surveys on the prevalence of deafness in the population. The most recent study for the United States was conducted by Webster, Himes and Lichtenstein (6). It was a test of the ability of 3666 people at the San Diego County Fair in 1948 to hear phonographically recorded pure tones. Steinberg, Montgomery and Gardner (7) reported results on the Chicago World's Fair hearing tests which were similarly conducted. Recently Wilkins (8) has attempted a study of the prevalence of deafness in England, Scotland and Wales. His methods were similar to those used by Beasley (9) in the National Health Survey in 1935 and 1936 and conducted by the United States Public Health Service.

He classified degree of impairment for an individual into 1 of 5 groups. In the first of these, the subject could hear speech at close range but had difficulty in group conversation. In the second, loud speech and conversing over the telephone were intelligible but direct conversation at close range was difficult. In the third stage, there was difficulty in understanding speech over the telephone at ordinary intensities but it was understood when amplified by a hearing aid or other means. Group 4 represented total deafness for speech, while group 5 was the deaf mute. Wilkins (8) has used a similar grouping for his survey of 1947 adding 2 additional groups but compared his results with those of Beasley (9) on the basis of his groups 3 to 7 inclusive. The percentage of deafness in the population as estimated by Wilkins was 3.9 per cent as compared to Beasley's 1.23 per cent. Attempts were made by Wilkins to explain this discrepancy between the two rates in the different countries. He has suggested that ability to hear telephone conversation (no telephones for most of his subjects) and the source of information (whether the informer was the one with hearing loss) might be responsible. Wilkins concluded from his analysis

that the incidence of deafness for different age groups was about 1 per cent at 20 years, 2 per cent at 35 years and 9 per cent at 65 years. In other words it could be considered as practically doubled with each fifteen years in advancing age. Beasley found, on the basis of average hearing loss of 47 db. or more for frequencies of 1024 and 2048 cps; a ratio of 1 in 103 males and 1 in 108 females between the ages of 35 to 45 years. In the period of 65 to 74 years, this ratio was 1 in 14 males and 1 in 18 females.

TABLE 1

Percentage of individuals with hearing loss greater than 45 db.

A comparison of San Diego County Fair (S D.F.) and World's Fair (W.F) data

In percentages

Age in years	Sex	440/880		1760		3520		7040
		S D.F.	W F.	S.D F.	W.F.	S.D F	W.F.	S D.F.
10–19	M	0.2	0.6	0.1	0.6	0.4	1.8	1.3
	F	0.2	0.6	0.4	0.4	0.6	0.3	0.3
20–29	M	0.0	0.1	0.0	0.3	5.0	2.7	6.7
	F	0 1	0.4	0.3	0.3	0.3	0.7	0.0
30–39	M	1.1	0.3	1.2	0.6	7 0	6.0	7.1
	F	0.8	1.2	1.4	0.8	0.6	1.6	1.4
40–49	M	1.7	1.4	3.6	2.6	13.0	16.0	13.9
	F	0.6	2.1	2.0	1.5	2.4	3.0	3.4
50–59	M	2 2	2.6	8.4	6.0	30.0	27.0	35 5
	F	0.7	4.0	2.2	3 0	2.7	7.0	6.1
60 and over	M	4.7		18.0		45.0		49.6
	F	1.2		9.0		13.0		23.6

The age periods of 30 to 40 years and over 55 years showed the highest incidence.

Hearing loss in a large sample of the population should be determined by methods somewhat similar to those used by Steinberg, Montgomery and Gardner (7) at the World's Fair in Chicago and Webster, Himes and Lichtenstein (6) at the 1948 San Diego County Fair. The latter used absolute thresholds for five frequencies (440 to 7040 cps.) and masked thresholds at two frequencies. Their results indicated that hearing loss is not normally distributed for the population as a whole. They found that absolute hearing loss, dispersion and skewness increased with age and frequency. A comparison of some of the data derived from the two studies is shown in table 1. The estimates are in percentage values for hearing

loss of over 45 db. for different age groups representing ten-year intervals. The results are in fair agreement, except for the 20 to 29 year old males, for frequencies of 3520 and 7040 cps. A plausible explanation for this discrepancy is discussed later under contributory factors. The greater number of males than females with hearing loss for high tones is apparent in this same age group and continues through the older age groups.

Types of deafness

Any of the various causes associated with hearing loss may occur in old age as with younger age groups although the incidence may be different. Associated with ageing and by far the commonest cause of deafness after 45 years of age is degeneration of sensory cells of the organ of Corti, spiral ganglion cells and peripheral nerve fibers. It is known by terms of perceptive, nerve and high-tone deafness. The hearing loss is characterized by a diminished or impaired hearing for tones bordering on the upper limit (approximately 4000 cps.) of the speech range and higher. The loss or degeneration of sensory elements in the cochlea extends from the basal turn into the lower and even middle portion of the second turn. This type of deafness is to be contrasted with middle ear or conductive deafness. Otosclerosis is a conductive form of deafness for which ankylosis of the footplate of the stapes in the oval window margin by atypical bone formation is the contributing factor. It is characterized by a loss of hearing for low tones but in well established cases of otosclerosis a hearing loss for high tones commonly becomes an additional factor (Walsh (10)). For this involvement of the peripheral neural mechanism of hearing such explanations as stasis of the endolymph have been offered. The ageing effects are no doubt superimposed in older individuals. A fact that should not be overlooked is the altered alignment of the ossicles in otosclerosis (Covell (11)). Guild (12) has recently emphasized the point that "interference with physical transmission of sound waves to the organ of Corti by conductive lesions often causes more impairment of hearing for high than for low tones." Cerumen or an ear plug are the simplest examples of a conduction impairment to be associated with a high-tone loss.

The phenomenon of auditory recruitment is of value for distinguishing between conductive and perceptive types of deafness. It measures hearing ability over a range of intensities well above threshold. The method of loudness balance consists of increasing the intensity of the tone in the affected ear until it is equally loud for both ears. This test presupposes some normal hearing. The difference limen tests measure the rate of change for loudness with increase of intensity and can be used with impairment in both ears.

Central processes become slowed down in old age with the result that

cortical interpretation for speech and sounds lacks alertness and concentration. Many aged people find it difficult to follow rapid speech in spite of little or no hearing loss. This is a form of central deterioration which needs further study.

Psychogenic or functional deafness is a type for which there is no anatomical basis. It is not to be confused with malingering, the pretense of deafness or the psychological effects of being deaf. The nerve impulses initiated in the peripheral organ reach the brain but they are not consciously heard. The importance of emotional states and other psychological factors on hearing have only recently been recognized. Morrissett (13) estimated that about 15 per cent of all cases of deafness treated in the army centers during World War II were psychogenic in origin. Hysterical and depression deafness (Ramsdell (14)) are types of psychogenic deafness. The problem is further complicated when psychogenic factors become superimposed upon an already existing hearing loss. The incidence of psychogenic deafness on an age group basis would be a study of considerable interest. Particularly is this true in view of the psychological aspects of ageing.

According to Silverman and Taylor (15) the value of hearing aids for the aged is questionable. Not only is deafness of the nerve type sometimes associated with confusion in hearing but older people do not have patience and learn less readily than younger ones. The proper use of a hearing aid depends on the ability of concentration. Psychologically, aged individuals are not good risks. De Maré (16) states that in perceptive deafness the difficulty in understanding speech is complicated by pitch distortion. Frequencies affected by the hearing loss and in the speech range appear to be lower or higher. A hearing aid further amplifies the distortion and leads to more confusion.

Hearing tests

The evaluation of hearing loss has come to be regarded in a more practical sense than previously. It is no longer a problem restricted to a diagnosis of the type of deafness and frequencies involved. The question is now asked: how well can an individual with a hearing loss adapt to his environment, society and occupation? A number of different methods have been devised for this purpose. These newer concepts and methods are dealt with in a recent book entitled *Hearing and Deafness: a Guide for Laymen,* edited by Davis (17). At present there is no extensive study on this or similar basis for the ageing individual and his hearing impairment. There is no doubt that such information will become available in the future. The ability of an older person to understand speech and the social adequacy of such a person with hearing loss are important factors to the problems of ageing. For this reason a brief description of some of the newer methods is included.

Earlier tests for hearing were primarily concerned with the sensitivity of the ear. Many of these were simple and quite crude, such as the ability to hear the voice, watch tick or click of two coins. The maximum distance at which these and other sounds could be discerned was considered a measurement of hearing. Tuning forks and still later the electric audiometer were used. It then became possible to map the frequency range of hearing. Tuning forks are still used in many instances as a rapid aid in the diagnosis of type of hearing loss. Their inaccuracy lies in the fact that the intensity of sound produced cannot be adequately controlled. The audiogram is a graphic representation of the measurement of hearing but it does not give all of the information to be desired. The ability to hear speech cannot be determined from the audiogram alone.

Many different speech tests are in present day use. Whether they are in words or sentences, they are qualified for familiarity and intelligibility. The Psycho-Acoustic Laboratories at Harvard University and the Bell Telephone Laboratories have developed such word and sentence lists. It is possible to measure the hearing loss for speech in two syllable words and the results are comparable with certain frequencies of the audiogram When the difference is considerable it is suggestive that psychological or other factors are involved.

For an appraisal of the understanding of speech the articulation curve has been developed (Davis (18)). It is the percentage of carefully selected words which an individual understands as they are spoken to him louder and louder. A person with a severe high tone deafness will not make a perfect articulation score because he fails to hear certain sounds. In spite of this his threshold for speech may be normal because he can hear the low frequency words.

Certain tests also measure one's ability to discriminate between two sounds which may be quite loud. This is not to be confused with the ability to detect a faint sound. In everyday life we are consciously or unconsciously interested in recognizing a particular sound or sounds in a background of noise of constant intensity. It is heard along with speech which is varied in intensity. Discrimination is tested in the low, high and middle frequency ranges.

Social adequacy is rated on the basis of the ability of an individual to follow ordinary conversation. Its borderline appears when there is a hearing loss for speech of 35 db. in the better ear. The average hearing loss is similar to that for the frequencies of 500, 1000 and 2000 cps.

Anatomical

As previously mentioned the results published in the literature on histological changes in the ear must be regarded, for the most part, with considerable skepticism. In view of this a detailed discussion at this time

does not seem justified. Only the more pertinent facts related to the different anatomical regions of the ear are considered. Their significance lies primarily in a better understanding of the physiology of ageing as it concerns the bone, soft tissues and specialized sensory organs of the ear. Many are irrelevant to the function of hearing but it is only through a consideration of all alterations that a final analysis can be made.

The temporal bone

One of the most important features of the temporal bone is pneumatization. An extensive literature is available on development of the air cell system and the factors related to the process. Less, however, is known of the influence of age upon these changes within the temporal bone. Wittmaack (19) believed that if the process had not been arrested in childhood it continued throughout life and, therefore, the most extensive pneumatic systems were found in the temporal bones of aged individuals. Others, Mündnich (20), Rainier (21), Vaheri (22), confirmed his viewpoint, while still others did not observe differences which could be correlated with age. Recently Ojala (23) reported on pneumatization in 89 temporal bones from 46 individuals varying in age from about 50 years to more than 90 years. He classified them according to Seppälä (24). Only 4 represented Group I (very extensive pneumatization reaching considerably beyond the mastoid process); 31 were classified under Group II (extensive pneumatization which extended throughout the mastoid process and to some degree also in squamous and zygomatic portions); Group III (pneumatization of the greater part of the mastoid process with sclerotic or diploic bone in the apex and sino-dural angle) was represented by 25 of the series; Group IV (pneumatization only in the region of the antrum) was represented by 17 of the temporal bones; Group V (no pneumatic cells apart from the antrum) was represented by 12 of the series. He concluded from his studies that advanced age did not produce any characteristic type of pneumatization. Asymmetric pneumatization was commoner and there was more irregularity of the air cell pattern with a slight tendency for decrease in extent of pneumatization.

While pneumatization is a physiological process which undoubtedly slows with maturity of the temporal bone, the factors which influence its extent through early life and into middle age are probably the same factors which might produce any changes in the air cell system for the aged. Among these are to be listed inflammatory and postinflammatory states, prolonged Eustachian tube occlusion, fibrosis of the mucous membrane and a variety of other so-called otitic processes. The minor alterations in the system which one might ascribe to old age may be an extension of these factors.

The otological surgeon is aware of the diminished ability on the part of the periosteal layer of the temporal bone and probably the endosteal bone to regenerate rapidly in older people. This has become of practical significance in the fenestration operation for otosclerosis. In order to retain its function in restoration of hearing the fenestra created by the surgeon must remain patent. Such is usually the case for older people but its closure by newly formed bone in young and middle-aged individuals remains a problem. Nylén (25) observed, from a study of otosclerotic foci in temporal bones representing various age groups, no instance in which only active lesions occurred over the age of 50 years. They were not uncommon in the groups up to the age of 50. This may not only indicate that otosclerotic bone is suppressed in further growth but that the enchondral layer in which the otosclerotic lesion occurs is affected by age.

Nager (26) found that osteoporosis of the temporal bone occurred in the aged and was most extensive in the periosteal layer but finally it involved the enchondral bone as well. The metabolic process of the enchondral layer and its resistance to bony diseases affecting other layers of the capsule is known.

There is evidence that the temporal bone may become more brittle in the aged and hence susceptible to fractures such as the microfractures described by Mayer (27), and the fracture of subaditus trabeculae (Guild (28)). Any additional structural change within the bone, if present in the aged, has escaped observation. The weaker stainability of the bony matrix in sections has been mentioned by Guild (1).

The external ear and auditory canal

According to Babbitt (29) the supporting cartilages of the walls of the external auditory canal undergo atrophic changes in aged individuals such that sagging of the skin at times is sufficient to diminish the size of the external orifice. The hairs in the outer portion of the canal become coarse in the male. It is probable that the layers of the skin show changes similar to those elsewhere in the body. Bonatti (30) described a greater number of elastic fibers in the fibro-cartilaginous portion of the canal. They were present at birth and increased somewhat through life to the time of old age for which period he found no regressive change in the elastic filaments. The ceruminous glands have been studied by Zorzoli (31) in 54 and 82 year old men. They were dilated and their contour was irregular. Low cuboidal epithelium lined the secretory portion in contrast to columnar epithelium of an active gland. In the specimen of the older individual the epithelium was pavement in type. The involutional process seemed to have no definite pattern of regularity because parts of a single gland were not always in the same stage.

The tympanic membrane

Zanzucchi (32) microscopically examined sections of the tympanic membrane from various age groups. At 51 to 75 years of age the substantia propria was thinner and sclerosing fibers were evident in the periphery and about the umbo. Elastic fibers were less obvious than for younger subjects.

The thickness of the membrane in the human according to Békésy (33) is about 0.05 mm. and it is not stretched but resembles a stiffened cone. He has described its elasticity as about 400 times smaller than the elasticity coefficient of pine wood. Békésy believes stiffening of the membrane improves the sensitivity and frequency range. According to him the effective area of the tympanic membrane is about two-thirds of its total surface, or 55 sq. mm. out of 85 sq. mm. A fold on its lower rim permits movement of the rigid conical portion as it turns on an axis of its upper rim. How these and other factors relative to the drum are influenced by the ageing process is unknown. It might be expected that an additional thinning of the membrane and sclerosis of its fibers could subsequently produce a less stiffened cone. Whether sensitivity and frequency range would be altered to any noticeable degree is doubtful.

The middle ear

The distribution of elastic tissue within the middle ear has been studied by Davies (34). It is present in the capsules of the ossicular joints, the ligaments which suspend the ossicles, the tendons of the intra-aural muscles and walls of the small arteries of the middle ear. Its distribution in the middle ears of ageing subjects is not known. The specimens in our laboratory do not show any significant variation in the amount of elastic tissue. Perhaps a larger series would reveal a definite trend in its distribution and occurrence. In the opinion of Davies, elastic tissue is important in maintaining the apposition of the ossicular chain and in addition it serves to suppress vibrations. Its presence in the tendons of the stapedius and tensor tympani muscles, he believes, assures a more gradual action on the part of the force generated by the contraction of the muscles.

The two muscles of the middle ear and particularly the tensor tympani undergo atrophic changes for a number of conditions including otosclerosis. Some atrophy is probably present with old age but it remains to be correlated with loss of hearing. The muscles in the cat and dog have been shown by Byrne (35) to consist of two types of fibers. He believes the striated fibers serve to hold the ossicular chain in a new position while the unstriated elements adjust the actual lengthening of the chain. It would be of considerable interest to know if there are two types of fibers in the human and if the atrophy of each type occurs simultaneously.

The ossicular chain may be regarded as a single unit made up of three

ossicles for which there is very little movement, if any, of individual osseous components. The joints between malleus and incus and incus and head of the stapes are firmly bound by capsules rich in elastic tissue. The articular surfaces are without synovial membrane; instead a fibrocartilaginous pad which bulges at the periphery of the joints fills the greater part of the intervening space. At points the poorly staining pad is attached to the articular cartilage of the ossicles. Fumagalli (36) presented evidence to show that the ossicular joints could be extensively damaged and the surfaces of the articular cartilages degenerated. He believes that such a process rapidly becomes an ankylosis in the malleo-incudal joint but this does not occur for the incudo-stapedial articulation. The latter, he maintains, does not undergo ankylosis because of movement. Degenerative changes in these small articulations may occur at any time during life, from infancy to old age. It is true that a greater number of these joint changes are to be found in the aged. They may be the result of trauma, gradual wear through use, heredity or other factors

Individual variations in position, weight and articulations of the ossicles are manifested to such an extent that Békésy (33) believes the small peaks that appear in threshold measurements may be due to these differences. His contention is further supported by the observation that very similar peaks are obtained for the two ears of the same individual.

The Eustachian tube

Calcification of the tubal cartilage according to Terracol, Corone and Guerrier (37) is not rare; however, it is less frequent in the aged than for other cartilages such as the laryngeal. They also noted that the fossa of Rosenmueller in the vicinity of the pharyngeal orifice contains a soft spongy tissue in the form of strands throughout its depth. These are not readily noticed on examination but on digital pressure the fossa becomes deepened and does not immediately resume its original appearance

Diameters of the isthmus of the tube with its cartilaginous and osseous support were measured by Wolff (38) in vertical sections at right angles to the long axis of the petrosae for individuals ranging in age from 2 days to 111 years. A considerably larger series has to be studied for the older age groups before any differences can be noted. Further studies on material relating to age should consider such factors as the type of epithelium, occurrence of folds and patency of the pharyngeal portion of the tube.

The inner ear

Stria Vascularis and External Spiral Sulcus. If the stria vascularis is the principal source of endolymph in the cochlear duct then any alterations in it associated with old age are to be regarded as of some importance.

A similar problem of fixation applies to it as does to the organ of Corti but to a lesser degree. The degenerative changes have been described for a number of different conditions including old age (von Fieandt and Saxen (39)). In their specimens from individuals 50 years of age or more they found very few chromophobe cells and were uncertain as to the number of chromophile cells present. The latter cell is in their opinion a secretory cell and also a supporting cell since the foot of it is anchored to the wall of a blood vessel. The chromophobe cell for man is poorly defined as compared to lower forms. They regard it as the precursor of the chromophile.

The cells of the external spiral sulcus area have been interpreted by von Fieandt and Saxen as possessing phagocytic properties. They are of the opinion that cellular debris in the cochlear duct is digested and passed into the capillaries of this region.

ORGAN OF CORTI. The work of Crowe, Guild and Polvogt (40) on histological examination of temporal bones from 79 patients who had their hearing examined in their last illnesses remains the only outstanding study of its kind. They reported atrophic changes of the organ of Corti in the basal turn and correlated them with a marked impairment for hearing high tones. In spite of this they could not demonstrate atrophic changes, or other lesions, greater than observed in control ears for normal hearing impairment accompanying age. The latter was determined on the basis of averages in the study by Bunch and Raiford (4) of hearing loss. This conclusion to their studies is to be seriously considered because of its implications.

The Otological Laboratories at Johns Hopkins University in Baltimore have at their disposal the most carefully prepared sections of human temporal bones available. It is likely that human material is unsuitable for this study in spite of the attempt to remove the petrous portion of the temporal bone as soon after death as possible and immerse it in fixative. Investigations under way in our laboratories have quite definitely proved to us that an animal's cochlea after immersion in fixative does not reveal in the finally stained and mounted sections the proper state of preservation of the cellular components of the organ of Corti. The hair cells and their immediate supporting cells are most vulnerable to autolysis. Such material is only of value when the cells are in advanced stages of degeneration or absent. Perfusion of the anesthetized animal with the fixative is essential before any judgment can be passed upon the appearance of the cells. Occasionally a perfusion will not flush all of the blood cells from the finer vessels. In these instances the difference in cell structure for the neighboring region of the organ of Corti is noticeable. In the opinion of the author the problem of high frequency loss with age is one which needs further

study of the peripheral sensory organ before searching the central areas for the explanation.

SPIRAL GANGLION CELLS AND PERIPHERAL NERVE. The spiral ganglion cells and cochlear nerve fibers are degenerated or lacking particularly for the basal turns in severe hearing loss for high tones in ageing individuals For less impairment of hearing fewer changes are to be found and for the ganglion cells the problem becomes one similar to that for the organ of Corti. Cytochemical methods, such as Hamberger and Hydén (41) used to ascertain the effects of acoustic stimulation on spiral ganglion cells, offer more promise than ordinary procedures. They successfully demonstrated an increased production and metabolism of ribose nucleic acids and proteins with sound and later extended their studies (42) to the vestibular ganglion using rotatory methods of stimulation. With repeated stimulation the total amount of nucleoprotein in the cells was considerably decreased.

Rasmussen (43) counted the fibers in cross sections through the human auditory nerve. He found the cochlear nerve to contain an average of 31,400 fibers with approximately 2200 less for specimens representative of ages 44 to 60 years. The vestibular portions of the nerve contained 1000 less fibers for the same group. In the selection of his material for study a history of normal hearing was necessary.

CONTRIBUTING FACTORS

At present it is impossible to accept any one or more factors such as have been proposed in explanation of the hearing loss which usually accompanies advancing age. The usual explanations, as discussed by Wolffheim (44), are progressive labyrinthine changes in the sense of wear and tear, atheromatosis associated with degeneration of the labyrinth, cochlear nerve and cerebrum; and, such factors as rigidity of the basilar membrane (Mayer (45)). The literature is filled with attempted explanations particularly on a clinical basis for the cause and relief of perceptive deafness accompanying old age. Hormonal factors may have a relationship but little is known of this phase of the subject. There are some who base their explanations primarily upon poor nutrition and stress the therapeutic value of vitamins. It is true that animals depleted of a particular vitamin, such as thiamine chloride, show characteristic manifestations and even degeneration of the cochlear nerve (Covell (46)). To correlate these findings with a hearing impairment of an elderly person is difficult. It is even more so when it is realized that the incidence of hearing loss among American soldiers released from Japanese concentration camps was no more than among the usual healthy troops (Day (47)).

Circulatory disturbances, particularly those caused by arteriosclerosis, within the ear or vessels supplying it have long been known to cause degenerative changes in the end organ. This is actually a pathological process for which lesions in the cochlea are demonstrable.

Asherson (48) has recently attempted an explanation of Menière's symptom-complex on the basis of interference with arterial supply to the cochlea. In a recent article Fowler and Fowler, Jr. (49) have discussed tinnitus and deafness in the light of work done by Knisely, Eliot, Block and Warner (50). The latter have demonstrated sludging in the smaller vessels elsewhere in the body and correlated it with severe illness, emotional states, ageing and so forth. The detailed distribution and structure of the terminal vessels which supply the cochlea are being studied in our laboratories by C. Smith. The presence of circulatory disturbances within the finer arterioles and capillaries of the cochlea, if demonstrable, may eventually explain some problems related to the ear.

Riesco (51) studied tinnitus and hypacusis in a group of 51 patients ranging in age from 50 to 70 years, with interesting conclusions. Thirteen of his patients had impaired hearing without tinnitus, 37 had impaired hearing with tinnitus, and 1 had no impaired hearing but tinnitus. He is of the opinion that cochlear alterations are not due to vascular changes but rather result from a degenerative and atrophic neuritis.

In the past few years our knowledge concerning perceptive deafness in infancy and childhood has been enlightened by the discovery of two different causes. The first of these is rubella, for which Carruthers (52) and others called attention to the relationship between maternal rubella in the first trimester of pregnancy and deafness in the child born subsequently. The infection in the mother has a deleterious effect upon the normal development of the organ of Corti in its early stages. The second discovery is that of severe neonatal jaundice associated with perceptive deafness. This jaundice, although not invariably associated with Rh iso-immunization, has been found by Perlstein (53) to cause deafness in about 40 per cent of the patients. Crabtree and Gerrard (54), for the one instance available for histological study, described a normal appearance of the organ of Corti, spiral ganglion cells and cochlear nerve fibers. Marked changes occurred in cells of the ventral and dorsal cochlear nuclei. It is findings such as these which will eventually be shown to have a bearing at least upon the incidence of [illegible] ay also aid in the explanation [illegible] ess (Altman (55)). To regard [illegible] the result of ageing processes [illegible] prenatal life through middle life are better understood.

Acoustic trauma is now recognized as occupying a more important posi-

tion than ever among the factors responsible for hearing loss. That it may be correlated with ageing is suggested by the studies of Perlman (56). He stated that older subjects are more susceptible to acoustic trauma and their auditory apparatus less recuperative than that of younger individuals The problem is one of immediate importance for all ages in industry and military life. It is of more than casual interest when one further considers the report of Webster, Himes and Lichtenstein (6). In their 20 to 29 year age group of males a greater hearing loss was in evidence than for a similar age group reported by Steinberg, Montgomery and Gardner (7). Seventy-two per cent of the former had worked or lived in a noisy environment. Lumio (57) in his studies of hearing loss of 203 railway engine employees in Finland reported audiometric measurements to show variations from normal in 78.8 per cent. The changes were directly proportional to age and years of service.

Davis, Morgan, Hawkins, Galambos and Smith (58) in their final report on temporary deafness following exposure to loud tones and noise found 4000 cycles to be more effective and 5000 cycles much less effective than 1000 or 2000 cycles in producing hearing loss. They exposed the ears of 15 men (17 to 21 years) and of 4 older men (29 to 46 years), at intervals of several days, to intense tones of 500, 1000, 2000 and 4000 cycles at intensities of 110, 120 and 130 db for periods varying from one to sixty-four minutes. They found recovery progressed rapidly at first but finally became very slow. It tended to be slowest for frequencies at about 4000 cycles. The greatest hearing loss occurred at a frequency half an octave above the exposure tone. Individual variation to susceptibility was apparent as well as occasional change in susceptibility on the part of the same individual on repeated exposures.

The otological literature following the last war has many reports on the effects of acoustic trauma of war for civilians and military personnel. No exhaustive study of these effects for relations to ageing has been attempted. Ogden (59) has recently published on the effects of gunfire upon auditory acuity as studied at the A. A. F. School of Aviation Medicine, Randolph Field, Texas. He found the noise of gunfire produced a hearing loss for tones of 2048 to 11,584 cycles among the gunnery instructors. There was no progressive loss for either the older students or instructors. The small age difference between instructors and students could not be stressed as significant although the former had a greater amount of hearing loss.

Summary

An impairment of hearing is no longer judged only by the inability to hear certain frequencies. The understanding of speech, the social adequacy index and psychological factors furnish important clues.

A high-tone hearing loss which increases with each decade of life, for most individuals, is characteristic of deafness in the ageing. Before it can be said that ageing is a cause of deafness a better understanding of the reasons for similar hearing loss for young and middle-aged groups is necessary. It is probable that impairment for high tones is established before the time of ageing and processes associated with it cause further deterioration. Acoustic trauma is to be seriously considered as one of the most important of the contributing factors for all age groups.

A marked high-tone hearing loss is characterized, histologically, by peripheral cochlear lesions. The attempts to demonstrate changes in the cochlea for moderate degrees of hearing loss have not met with the same success. Artefacts described in the literature as alterations due to age are for the most part the result of autolysis. A study of human temporal bones cannot reveal the cytological detail necessary to evaluate changes and correlate them with function. Studies on a large series of animals of different ages for which the hearing could be tested by newer physiological methods offer an approach to the problem.

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11

THE HEART AND GREAT VESSELS IN OLD AGE

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The problem of the condition of the heart and great blood vessels in old age had best be considered under three headings: first, diseases of the heart and great vessels which usually or often begin in early or middle life and are still present in old persons; second, the kinds of cardiovascular disease that are predominantly found in old persons; and third, the process of ageing as it involves the heart and great vessels, not necessarily a part of any of the types of heart disease customarily recognized.

DISEASES OF THE HEART AND GREAT VESSELS WHICH CAN BE FOUND AFTER THE AGE OF 60 YEARS

Every single kind of heart disease which may be encountered in the earlier decades of life can still be found in old age but usually in quite different degrees. Thus, some of the diseases that are relatively common in young people are infrequently or rarely found in old age while some conditions infrequently or rarely found in young people are much more commonly found in old age, and a few of the least common cardiovascular diseases seem to have much the same incidence in youth as in older persons.

Congenital cardiovascular defects

Congenital cardiovascular defects which are commonest during the first year of life, and from which fully half of all infants so afflicted at birth succumb before the age of 1, decrease steadily in incidence from early childhood to middle age; relatively few are long-lived, and after the age of 60 one encounters congenital cardiovascular defects very infrequently (1).

Those deformities of the heart and great vessels which produce cyanosis and clubbing in childhood, in other words, the causes of the morbus caeruleus or maladie bleue, are so serious that most persons so affected die

before the age of 30. The two conditions which are associated with cyanosis and clubbing due to right to left shunts which have been reported as permitting survival to the age of 60 or a bit beyond are: (1) the tetralogy of Fallot (one case aged 61 has been recently encountered) (2), and (2) the syndrome of pulmonary stenosis and auricular septal defect (one case was recently reported by the author of this chapter succumbing at the age of 75, eighteen years older than the previous record case) (3). Doubtless there are other survivors with the maladie bleue not yet recognized or reported, but there are certainly not many.

No case so far as I know is on record with the morbus caeruleus who survived to the age of 60, either with Eisenmenger's complex, with transposition of the great vessels, with a triloculate or biloculate heart or with any other rare anomaly resulting in a right to left shunt.

The noncyanotic types of congenital cardiovascular disease allow survival to old age but even these cases are uncommon. Patients are on record who have done well and are still alive at advanced ages with patency of the ductus arteriosus (I have one such patient in excellent health, working hard and playing golf at the age of 75) or coarctation of the aorta (the oldest case on record was 92 years old with complete closure of the aorta and a ventricular septal defect (4)).

I know of only very rare cases with an auricular septal defect with or without mitral stenosis living to the age of 60 although a good many have been noted to have reached the middle fifties; nor have congenital uncomplicated valvular defects, in particular congenital pulmonary or infundibular stenosis and congenital aortic stenosis, permitted survival into the seventh decade, so far as I am aware.

The reasons for the hazard to life produced by congenital cardiovascular disease are several. In the first place, in the cyanotic cases anoxia is a very limiting condition, acting on the brain as well as on the rest of the tissues of the body, and inasmuch as very cyanotic cases have very high red blood cell counts with markedly increased viscosity of the blood, intravascular thromboses are common and are not infrequently a cause of death.

A second factor limiting life in congenital heart disease is the common occurrence of acute or subacute bacterial infections, producing endocarditis or endarteritis, previously uncontrolled by antibiotics and now not infrequently, although not always, cured by penicillin or similar new remedies. Such a complication can take place at any age and may be overlooked in old persons.

A third reason for the limited longevity in congenital heart disease is myocardial failure from the strain of valvular or other obstruction or from pulmonary hypertension secondary to pulmonary vascular disease that can complicate some congenital defects. Thus, congenital aortic stenosis

or coarctation of the aorta with the accompanying hypertension may result in left ventricular failure, while pulmonary stenosis may lead to right ventricular failure; large patency of the ductus arteriosus may result in failure of both ventricles.

Other less common causes of death in congenital cardiac patients before old age is reached include rupture of the aorta secondary to coarctation, cerebral embolism or abscess resulting from the passage of clots, aseptic or septic, through an interauricular septal defect, and pulmonary thrombosis or secondary infection superimposed on the pulmonary vascular disease which in turn results from certain congenital defects.

• It is very important for the physician to be aware that it is possible for old persons to suffer from congenital cardiovascular defects and on occasion to search for them by all the diagnostic measures available.

Rheumatic heart disease

Rheumatic heart disease is found more frequently than congenital cardiovascular defects in old persons. In fact, it is not rare to find either mitral or aortic valve disease in a person of 60 to 65 or even 70 years old which has been present ever since childhood; usually it is of less marked degree than the average, but nevertheless it may be clearly diagnosable. The commonest lesions so found are mitral stenosis of slight to moderate degree, aortic stenosis of slight to moderate degree and aortic or mitral regurgitation of slight or very slight degree. I know of no patient with free aortic regurgitation due to rheumatic involvement or with very marked mitral regurgitation of similar etiology who has lived to be older than 60 years. Pulmonary valvular disease due to rheumatic fever is so rare that it need not be considered; I am sure that it has not been found in old age. Tricuspid stenosis, however, has been noted associated with mitral stenosis in a few patients over 60. Recently the author, with associates, has reported the case of a patient aged 61 who had lived with chronic congestion and ascites (5) for many years and finally succumbed not to heart failure but to peritonitis.

The reason survival to an advanced age with rheumatic heart disease is possible is that the lesser defects present relatively slight burdens to the heart and circulation. One of my most notable patients was an aged doctor in whom a diagnosis of mitral stenosis was made first at the age of 79 years when he suffered from angina pectoris while playing golf. At the age of 82 he died of pneumonia, and at postmortem examination a clear-cut slight to moderate degree of characteristic mitral stenosis was found with very little heart burden therefrom. Even the left auricle was but very slightly enlarged. The rhythm had been normal throughout life and there had been no handicap from this disease, which undoubtedly had started

in childhood although never found until late in life (6). If the heart is not much enlarged and if the rhythm remains normal, rheumatic heart disease presents only two hazards.

In rheumatic heart disease one of the chief hazards in childhood and early youth is that of recurrence of the acute rheumatic process, the effect of which on the myocardium is to produce a myocarditis and cardiac dilatation, sometimes with failure or death. The myocarditis is often more important than the endocarditis or pericarditis that may be part of the process. At older ages there is fortunately less likelihood of active rheumatism. On the other hand, such is possible and I myself have encountered several patients with active rheumatism superimposed on rheumatic heart disease in old age. Two that I remember quite clearly were 66 and 73 years old respectively at the time of the acute rheumatic fever.

The other hazard is that of the special disease to be discussed next.

Subacute bacterial endocarditis or endarteritis

Subacute bacterial endocarditis or endarteritis is a common complication of congenital and rheumatic heart disease in youth. Even though both congenital and rheumatic heart diseases become infrequent in old age, subacute bacterial endocarditis and endarteritis remain as hazards. They are, however, likely to be overlooked because the reaction of the older person to this bacterial invasion may be relatively mild. Death may supervene after a long illness which may not have been clarified. Certainly blood cultures and other careful studies should be made in an older person, as well as in a younger, when there are unexplained fever and weakness in the presence of rheumatic heart disease or congenital cardiovascular defects. Fortunately the treatment when instituted early is usually successful in the majority of cases, old or young. Penicillin, streptomycin, and other curative preparations now available should be given in ample amounts as needed.

Cardiovascular syphilis

Fortunately cardiovascular syphilis is on its way out, since very little new disease of this sort develops in a civilized community where syphilis is prevented or recognized early and treated. However, on occasion, some patients with aortitis with or without aneurysm or aortic valve involvement may live beyond 60, especially if their infection is acquired late in life. Thus an individual who acquires syphilis at the age of 45 may have a maximal effect from it at the age of 65, not discoverable before the age of 60. It is important always carefully to examine individuals above the age of 60 who show aortic regurgitation or wide aortas for the presence of syphilis as the etiological factor. If it is found it should be treated, nowa-

days preferably with penicillin in moderate dosage, even though there are no symptoms or much of any strain from the lesion or even if there is extensive heart failure. It used to be thought hazardous to use specific antisyphilitic therapy in the presence of heart failure but now one may safely treat both the heart failure and the active process simultaneously if penicillin is employed (7).

Other infections or infestations

Other infections or manifestations such as diphtheria or trichinosis may involve old persons as well as young but serious cardiac disease secondary thereto is rare.

Endocrine disease

Endocrine disease may be attended in old age as well as in youth by cardiovascular involvement. Perhaps the most obvious and common difficulty of this sort is that developing from thyrotoxicosis. It happens that not very rarely old persons may be found to have carried a mild thyrotoxic state for ten to twenty years or even longer and to have developed therefrom an arrhythmia usually consisting of auricular fibrillation with a good deal of tachycardia, cardiac enlargement and sometimes actual failure. The important lesson to be derived from these cases is that we should always think of the possibility of thyrotoxicosis in an otherwise unexplained case of cardiac enlargement with arrhythmia and with or without failure. Often the physical examination and symptoms suffice for the diagnosis but on occasion it is necessary to make specific tests for the disease. It is of great importance to establish the correct diagnosis because of the ready therapy available either by operation or medically with thiouracil, irradiated iodine or potassium iodide. Digitalis in such cases is likely to be much less important than the therapy directed to the thyrotoxicosis itself although both may be given together.

Myxedema, an uncommon disease at any age, is attended by a depression of cardiac activity and often by enlargement of the heart with but rarely any gross failure.

Hypertension

Systemic hypertension is a very common cause of heart disease in old age as it is in middle age, although probably no more common, inasmuch as some of the patients more severely hypertensive will have died before the age of 60, while many old persons can carry a mild hypertension without any heart disease from it. Nevertheless, hypertension is one of the most common of all diseases after the age of 60 and along with it there is often found left ventricular enlargement with or without failure. In a hyper-

tensive patient a careful follow-up program with analysis of symptoms and signs, and especially serial electrocardiography to note the beginning of strain and enlargement of the left ventricle is of paramount importance. Increasing height of the R waves and lowering to inversion of the T waves in the classical Lead 1 and in the precordial leads over the left ventricle, in particular V_5, are generally the first clues to the beginning of the "hypertensive heart". Treatment, of course, should be directed so far as possible to control of the hypertension itself. More will be said about this disease in the next section of this chapter.

Cor pulmonale

The cor pulmonale, acute or chronic, is secondary to pulmonary hypertension, which in turn is due to obstruction in the pulmonary circulation not caused by disease of the left heart chambers. Thus, the acute cor pulmonale consists of an acute dilatation of the right ventricle, almost invariably the result of massive pulmonary embolism, while the chronic cor pulmonale is secondary to fibrosis or silicosis of the lungs with constriction of the blood vessels therein or to endarteritis obliterans.

Doubtless both the acute and chronic types of cor pulmonale are overlooked, especially if they are of mild degree. They occur not infrequently, especially the acute cor pulmonale in the older age groups in which leg vein thrombosis and pulmonary embolism are much more common than in youth; in fact leg vein thrombosis with pulmonary embolism is one of the chief hazards of old age and a common cause of death (8). There may or may not be acute dilatation of the right ventricle (the acute cor pulmonale) attending pulmonary embolism (9, 10).

The chronic cor pulmonale is to be recognized largely by electrocardiogram and a history of chronic pulmonary disease of one sort or another. Treatment in either case is difficult. Prevention of further damage is the important therapy, as for example, the use of anticoagulants and leg vein ligation to prevent further pulmonary embolism in the acute cases. Better ventilation of environments of industry and guarding against infection are the important measures to protect the individual with the chronic cor pulmonale who is growing older. When the right heart fails, the treatment is the routine one for myocardial insufficiency, that is, the application of rest, digitalis, low sodium intake and mercurial diuretics.

Coronary atherosclerosis

Next we come to the most difficult problem of all in older age groups, namely that of coronary atherosclerosis producing serious heart disease as evidenced by the symptom of angina pectoris, characteristic electrocardiographic abnormalities or the occurrence of acute myocardial infarc-

tion. Many serious cases of coronary heart disease begin in the forties and a considerable number succumb before the age of 60. These are perhaps the most fulminating instances and are chara [illegible] weight, mesomorphic [illegible] type showing a hig [illegible] without a good deal of endomorphy (that i [illegible] build) and with very little if any ectomorphy (characteristic of the thin build) (11) Coronary atherosclerosis is a disease per se and not simply a manifestation of old age although it does come commonly in older persons after the age of 60 More will be said of this important disease in the second part of this chapter.

Miscellaneous types

There are a few miscellaneous types of heart disease that may be passed over quickly in concluding this part of the chapter. They are either rare or unimportant per se. Among such are (a) neoplasms of the heart, great vessels, and pericardium, extremely rare, usually metastatic in origin [illegible] very difficult (although on occasion possible [illegible] disorders such [illegible] because of th [illegible] and coronary vessels; and (d) certain blood [illegible] such as severe anemia which may involve the heart itself.

Before leaving this section of the chapter [illegible] the decreasing [illegible] as age advan [illegible] the age of 60 remain apprehensive [illegible] heart whether there is any heart disease or not, they are usually less so than in earlier ages, for at this age many persons have become resigned or philosophical about the situation and are no longer in the nervous state that they were twenty, thirty, or forty years earlier at the time perhaps of the first discovery of a heart murmur, an arrhythmia or an increase of blood pressure.

Cardiovascular Diseases Characteristic of Older Persons

The cardiovascular diseases that are characteristic of older persons are few in number despite the fact that many other kinds of diseases of the heart and great vessels continue to be found, although in decreasing numbers, in old age. The two important diseases that increase with age are hypertensive heart and aortic disease and coronary atherosclerosis with insufficiency and with or without actual myocardial infarction. Congenital cardiovascular defects, rheumatic heart disease, bacterial endocarditis, cardiovascular syphilis, thyrotoxic heart disease and the cor pulmonale are diseases of earlier and middle life rather than of old age.

Hypertensive heart disease

Malignant hypertension kills in youth or middle age; it is rarely a problem in old age. On the other hand there are a good many instances of hypertension with various degrees of deleterious effect on heart or blood vessels which increase in number steadily to a moderately advanced age such as 75; there are relatively fewer in extreme age. The frequency of trouble from hypertension in old persons is partly due to the added effect of arteriosclerosis itself.

With loss of elasticity of the aorta, atherosclerotic changes therein and hardening of the other larger arteries, there is frequently a systolic hypertension without much of any increase of diastolic pressure. Although the work of the heart is increased by such a change, the strain thereon is relatively slight compared to that produced by the greater diastolic hypertension common at earlier ages. The heart does tend to enlarge with the passage of many years of the type of hypertension dependent largely on arteriosclerosis, and actual failure may eventually ensue when the heart weakens in senility, but the strain is more marked on certain blood vessels, particularly those of the cerebral circulation, with the occurrence of apoplexy from cerebral hemorrhage, in major part due to the very large pulse pressure. An example of such a case would be that of a man or woman aged 75 years who has a systolic pressure of 220 mm. mercury and a diastolic pressure of 100.

The large group of hypertensive patients intermediate between those with malignant hypertension in youth and middle age and those with the arteriosclerotic, relatively unimportant, type of hypertension, presents the main problem of high blood pressure in old age. Many patients have both systolic and diastolic hypertension starting in middle age and extending well beyond 60 before termination of life, which is usually on a cardiovascular basis from heart failure, complicating coronary heart disease, apoplexy, arteriosclerotic nephritis or, rarely, dissection of the aorta. Men and women are about equally numbered in this group. At early ages the male is much harder hit by the effect of hypertension than is the female but by the age of 60 many hypertensive males have succumbed.

Fortunately, older persons who have hypertension with important secondary effects on heart or blood vessels have, as a rule, less severe strains, physical and nervous, to bear than those to which they were subjected ten or twenty years earlier. Therefore, they can as a rule live a life better [illegible] hypertensive strain and so may carry on useful and com- [illegible] obesity to be [illegible] be treated as [illegible] nuous specific measures like sympathectomy or the rigorous rice diet are in order. If the

hypertensive heart is large after the age of 60, it is probably wise to institute the regular use of tonic treatment with digitalis, perhaps a daily dose of 0.1 to 0.2 mg. of digitoxin, averaging 0.15 mg., or 0.06 to 0.1 g. of powdered leaf daily without necessarily digitalizing first. Of course, if failure comes, then the treatment should be that of the usual routine measures for myocardial insufficiency.

Finally, we should add the observation that we do not yet know the normal limits of blood pressure in each decade of life. Some have believed that the blood pressure should not rise with increasing age. On the other hand, since many apparently normal persons in older ages have some elevation of blood pressure, Master (12) has believed that we may rightly consider the old dictum of a normal systolic pressure of 100 mm. mercury plus the age of the person as being reasonably correct. At any rate a blood pressure of 160 systolic and 90 diastolic can be considered normal enough in a man or woman 65 years old.

Coronary heart disease

It is normal for coronary atherosclerosis gradually to increase with advancing years. The abnormality comes when the degree of coronary atherosclerosis is enough greater than the compensation afforded by an inadequate collateral circulation to cause symptoms or obvious signs; but happily it is also normal for a collateral circulation to develop rapidly enough to keep pace and so to bypass possible points of obstruction. There may be actually only a small percentage of difference in the amounts of coronary atherosclerosis in a healthy man of 65 and in his neighbor of the same age who has angina pectoris or who has suffered acute myocardial infarction. There is by no means, as some have thought, 100 per cent difference. Also on occasion, superimposed on a degree of coronary atherosclerosis that is perhaps not out of keeping with one's years, there may be some sort of an accident or coincident illness which precipitates a thrombosis in one of the sclerotic coronary arteries which may then in turn cause acute illness or death. Hence in older persons it is generally wise to avoid sudden, excessive physical strain or emotion or indulgence in the ingestion of large amounts of food or alcohol It is true that from the age of 60 on, at least up to the age of 90, both men and women show increasing numbers afflicted by angina pectoris, coronary thrombosis or electrocardiographic changes consistent with limitation of coronary blood supply. Some of this coronary arteriosclerosis may be attributed to the ageing process itself but some is doubtless due to defects in fat or muscular metabolism similar to those that take place in susceptible individuals in the thirties and forties. As to what age one may expect coronary atherosclerosis of important degree to appear normally we have no accurate information as yet.

Certainly, as noted above in speaking of hypertension, so in the case of coronary atherosclerosis itself the custom of older persons to live quieter lives enables many to support coronary heart disease with reasonable comfort while carrying on useful lives for many years. Frequently there is complete recovery from coronary insufficiency as age advances. I have known many individuals who were much better, or indeed quite well, at the age of 70 or 75 years in contrast to their ill health because of coronary heart disease at the age of 60 or 65 (13).

The Process of Ageing as It Involves the Heart and Great Vessels

This part of the chapter is by far the most difficult, for several reasons: (a) much less is known about the process of ageing of heart and great vessels than about the actual diseases that involve these structures; (b) it is extremely difficult to distinguish the effect of ageing per se from the effects of diseases that afflict any individual throughout a long life, (c) it is rare for a person to die of old age alone. A generation ago a common primary diagnosis on death certificates of men and women dying after the Biblical age of three score and ten or even in the sixties was senility or old age or arteriosclerosis, without any careful study of the possible presence of specific disease processes such as coronary thrombosis, cerebral vascular lesions, other circulatory diseases, for example pulmonary embolism, or even carcinomata or infections. Autopsies were infrequently carried out in old persons and so these common diseases were missed. In recent years, however, more careful scrutiny has revealed the fact that the vast majority of aged persons die of readily recognized lesions, including bronchopneumonia, which despite the advent of the antibiotics can still remain "the old man's friend".

Nobody lives a long life completely free from acute illnesses, especially colds, accidents, and strains of one kind or another. No one knows with any degree of certainty what effect, perhaps only infinitesimal each time, any such factor may produce in myocardium, endocardium, or arterial or venous intima, media or adventitia. Repeated insults such as simple colds may conceivably hasten somewhat the so-called ageing process in any given individual, and serious diseases such as diphtheria, typhoid fever or hypertension may do more. Even though octogenarians may have weathered much illness of one kind or another they may not live so long as they would have done had they been totally healthy all their lives; their lives may stop at 90 instead of reaching the century mark. Who knows? No one as yet, but with the coming of increasing prophylaxis of disease, accidents and strains in future decades and centuries, we, or more likely our descendants, may some day find out. And it is of course our aim not merely to add years to life but life to years.

Inheritance certainly plays as large a role in longevity as does environment with its exposure to the particular diseases most common in any particular part of the world. The constitution passed on from generation to generation consists of the ensemble of body tissues, strong or weak, and of the effect thereon of variations in activity of the internal organs of secretion and of central nervous influences. Thus, a high normal basal metabolic rate appears to be conducive to less wear and tear of arterial wall, especially in the shape of intimal atherosclerosis, than does a low rate even though the latter is considered to be within the normal range. A weakening of the media of the aorta, the so-called medionecrosis of Erdheim, of unknown cause but perhaps based on a congenital defect, favors dissection of the aortic wall when hypertension is superimposed. There is in all this much to learn.

Despite all these difficulties, however, some knowledge exists as to the ageing of tissues, both of experimental animals and of man. How much limitation of longevity is imposed by such tissue ageing in the absence of obvious disease processes remains uncertain. There are widely recognized senile changes, as pointed out by Carlson (14): gradual retardation of cell division, of capacity of cell growth and of tissue repair; gradual retardation in the rate of tissue oxidation (lowering of the basal metabolic rate), cellular atrophy, degeneration, increased cell pigmentation and fatty infiltration; gradual decrease in tissue elasticity and degenerative changes in the elastic connective tissue; decreased speed, strength and endurance of skeletal neuromuscular reactions; and decreased strength of skeletal muscle. It seems probable that cardiac muscle is affected by these senile changes in much the same way as is skeletal muscle.

Specifically the myocardium in extreme old age shows some atrophy with shrinkage of muscle cells, brown pigmentation, decrease of cross striations and interstitial fibrosis if there is in addition considerable decrease in coronary blood supply. Arrhythmias of benign type are common, in particular extra-systoles or premature contractions, paroxysmal auricular tachycardia and paroxysmal or constant auricular fibrillation. These disturbances of rhythm are, however, relatively unimportant as a rule if [illegible]

rhythmias much of the time, but the typical senile heart is not a large organ. Frequently in old age the heart seems, on x-ray examination, actually smaller than it is because of its vertical position in association with chronic pulmonary emphysema and with a low level of the diaphragm so often found in older persons.

Probably more important than the ageing state of the myocardium itself is the concomitant ageing of the rest of the body, in particular of

the endocrines and nervous system. Finally, there is no drive left and the heart may falter not because of intrinsic weakness but because like the "one horse shay" collapse occurs in the whole individual in all its parts. Such an ending to life is, however, very much rarer than *that due to some* common complication, namely, a vascular accident or an infection which the aged body can no longer resist.

The endocardium, particularly that of the valves, becomes thickened in old age and often spotted by atheroma, but except in cases of a real disease entity called Mönckeberg's sclerosis (calcification at the valve base, in particular, the aortic), there is no interference with function.

Finally, the walls of the great arteries, of the aorta preponderantly, slowly lose their elasticity and become dilated and elongated. In extreme cases there may be in advanced old age a diffuse aneurysmal dilatation of the aorta, called senile ectasia, that resembles clinically the syphilitic involvement of the aorta in youth and middle age and may likewise end fatally by rupture (16). The loss of aortic elasticity cuts down the functional capacity of the circulation appreciably in old individuals without actual disease.

It is to be recalled that full efficiency of the circulation of blood depends on more than the heart alone (15, 17). The aortic elasticity is of much importance in converting the systolic ejection of blood from the heart into an even flow throughout the body. When the aorta becomes more rigid it *acts like a pipe and the pulse pressure increases along with the systolic* (and not the diastolic) pressure; this is the so-called arteriosclerotic hypertension already referred to which although not much of a strain on the heart can be something of a hazard for brittle vessels in the brain.

There are two other accessory aids to the heart's function that should be considered besides the elasticity of the walls of the great arteries. Good tone of the skeletal muscles, especially of the extremities, helps to force blood back to the heart if the valves in the veins are competent. The better the state of these muscles therefore, the better the circulation of blood in any given individual. One of the best ways to maintain good muscle tone in old age is through the maintenance of healthy exercise right through life. This better peripheral circulation also tends to reduce stagnation and thrombosis in the leg veins, which is one of the greatest hazards postoperatively or indeed in medical cases after the age of 60 years.

The third accessory which aids the circulation of blood is good diaphragmatic respiratory excursion and tone. The diaphragm acts not only to suck air into the lungs on inspiration but it also draws blood into the great [illegible] When proper diaphragmatic action [illegible] r poor tone, there is not so good a [illegible] for advising regular exercise

throughout life, avoidance of obesity and prophylaxis and proper treatment of infections of bronchi and lungs, and of asthma.

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12

HEMATOLOGIC VALUES IN THE AGED[1]

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Information about the normal range of hematologic values in elderly people is incomplete. Many of the published reports record data for only a small number of subjects, deal largely with erythrocyte and hemoglobin levels, fail to describe methods used, and ignore qualitative morphologic changes. There have been almost no systematic studies of the total blood volume, of the various factors related to hemostasis, and of reticulocyte percentages. Furthermore, observers have found it difficult to select, from persons above the age of 60 years, a representative sample of the population, free of disease except for those degenerative changes which may be considered "normal" in the aged. For these reasons, the material summarized in this chapter can only indicate either: 1) the approximate range of normal values, or 2) the areas where information is particularly scanty. A few of the published reports have not been included in the tabulations because description of methods or of subjects was inadequate. Data obtained from the literature have been supplemented by observations made in this laboratory on the blood of 50 men and 50 women, 60 years of age or older.

MATERIAL AND METHODS

Fifty male and 50 female subjects ranging from 60 to 95 years of age were studied. Their records indicated that they were free of any known or recognized disease except for degenerative changes, e.g., arteriosclerosis, atrophic skin, degenerative arthritis. A few showed some of the complications of these changes such as Parkinsonism, residual hemiparesis, mild essential hypertension and mental deterioration. One had mild, well-con-

[1] The investigative work published in this chapter was supported by Research Grant H-22 from the National Heart Institute, United States Public Health Service.

trolled diabetes. The Kahn was negative in all subjects; the NPN slightly elevated in a few. Most subjects were inmates of the St. Louis City Infirmary; a few were patients in the Barnes Hospital.

Oxalated (1) venous blood, obtained without stasis between 5:30 and 6:30 a.m., before the subjects had gotten out of bed or had been served breakfast, was used for all determinations except differential, reticulocyte, and platelet counts. Preparations for the latter were made from free-flowing capillary blood. Pipettes and hemocytometers standardized by the U. S. Bureau of Standards were used for the red and white blood cell counts. Hemoglobin was determined as oxyhemoglobin with a standardized Evelyn photocolorimeter (2). For packed red cell volume, blood was placed in a Wintrobe tube and centrifuged for 30 minutes at 3,000 r.p.m. Reticulocyte and platelet counts were made by the wet technique, using Dameshek's method (3). Coverslip preparations for differential counts and cytologic study were stained both with Wright and supravital stains. Sedimentation rates were read at 60 minutes in Wintrobe tubes, and were corrected for variations in the packed cell volume (1).

Bone Marrow

During childhood, there is a gradual decrease in the amount of red, hematopoietically active marrow with a concomitant increase in yellow or fatty marrow. The extent to which this process continues after adult life has been reached, particularly in the aged, is not known with certainty. Custer and Ahlfeldt (4) attempted to obtain such information by studying the cellularity of the marrow obtained during 100 autopsies, including 19 done on persons above the age of 60 years. They cautioned that their results were only approximations, and presented them in graphic form (fig. 1). The graphs, however, suggest that there is a slight tendency for the marrow in the flat bones to become progressively less cellular with advancing years.

Most studies have been made on marrow aspirated from a single bone, and must be interpreted with caution because the specimens obviously provide inadequate sampling of the whole marrow volume. Reich, Swirsky and Smith (5) concluded, from observations on sternal marrow aspirated from 100 subjects of both sexes between the ages of 65 and 95 years, that the bone marrow is relatively unchanged in the aged and in some instances may actually show increased cellularity. Sacchetti (6), in 26 cases 63 to [illegible]

also an increase in lymphocytic elements. Cheli and Giordano (7) examined marrow specimens from 21 patients (60 to 90 years); they found no con-

stant decrease in cellularity and in some instances observed an apparent stimulation. Plum (8) was not able to detect any definite relationship between age and the cellular composition of sternal marrow. Segerdahl (9), however, described a decrease in the number of active bone marrow cells which she thought was due to the increasing number of fat cells.

About the only conclusion one can draw from the published reports is that there probably is a tendency for the ratio of red to fatty marrow to decrease in people of advanced age; no other significant change has been observed.

Total Blood Volume

Published data on the blood volume in old age are extremely scanty. Gibson and Evans (10) included 7 men and 3 women above the age of 50 years in their series of 90 subjects on whom blood volume was determined by the dye (T-1824) method. When all of their results were analyzed by decades, there seemed to be a tendency for average values to decline with

advancing years. The decrease in women after the fourth decade averaged 16 per cent below middle age values, while in men it was 8 per cent

Cohn and Shock (33) utilized the T-1824 dye method with ten minute sampling to determine the blood volume on 60 normal males above the age of 50 years. The mean plasma volume was 48.0 cc. per kilogram body weight with extreme values of 31.29 and 62.47 cc. The range in total blood volume was from 54.33 to 100.6 cc. per kilogram of body weight The mean values by decades for the total blood volume were (in cubic centimeters per kilogram): 86.09 from 50–59 years; 78.33 from 60 to 69 years; 80.71 from 70 to 79 years; 82.84 for 80 years and over. There was in these studies, therefore, no significant change with increasing age. The total number of observations, however, is still too few to permit any generalizations.[3]

Erythrocyte Values

Investigators who have studied the blood in people of advanced age have focused their attention more on the erythrocyte than on any other component. A composite summary of the thirteen most extensive studies is given in table 1. Also included for comparison are the values reported by Wintrobe (11) and by Osgood (12) for red cells and hemoglobin in healthy young adults.

Close inspection of the data tabulated in table 1 shows that the range of variation from minimum to maximum values is greater than usually is obtained in similar studies made on younger age groups. This fact suggests that subjects were included who had diseases other than those common to the ageing process. From the published reports, it is also evident that there was considerable difference in the technical care used by various workers in the collection of data. Furthermore, some of the results indicate that erythrocyte values are lower in persons above the age of sixty years, while others failed to show such a difference. For instance, Newman and Gitlow (13), Fowler, Stephens, and Stump (15), Miller (16), Millet and Balle-Helaers (19), and Rud (20) concluded that the red blood cell counts were less than in young adults. These same workers, with two exceptions (19, 20), also reported lower hemoglobin values. Olbrich (14) found a slight decrease in the erythrocyte and hemoglobin levels in elderly males but noted no essential change in women. Our own results were similar. Hansen (18) stated that the hemoglobin may fall slightly in older people without there being an associated change in the red cell count, but cautioned that

[3] This change may be secondary, in part at least, to the decreased testosterone secretion in elderly males. The subject has recently been reviewed by Hamilton (Hamilton, J R , Role of testicular secretions as indicated by effects of castration in man and by studies of pathological conditions and short life span associated with maleness. Recent Progr. Hormone Research 3: 257–322, 1948.).

TABLE 1

Erythrocyte values

Author	Age range	Sex & no. of cases*	RBC millions/mm³			Hb (gms. or %)			Reticulocytes (%)			Packed cell volume (%)			MCV (cu microns)			MCHb (micromicrograms)			MC Hb. conc (%)			Hb method
			Max.	Min.	Mean	Max	Min.	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	
	yrs																							
I. Values for normal young adults																								
1. Wintrobe (11) (max. & min. = range of normal)	M. & F., adults	M. 544 RBC 583 Hb. 381 PCV	6.2	4.6	5 4	18	14	16				54	40	47	94	80	87	32	27	29 5	38	33	35	Newcomer
		F. 387 RBC 433 Hb. 313 PCV	5 4	4 2	4.8	16	12	14				47	37	42										
2. Osgood (12)	M. 14–30+ F 14–30+	M. 259 RBC 259 Hb 153 PCV	6 2	4.6	5.42	18	14	15.8				50	40	44 8	—	—	—	—	—	—	—	—	—	Osgood-Haskins
		110 Retic							3 0	0.5	1.46													
		F. 152 RBC 152 Hb. 108 PCV 50 Retic	5.4	4.2	4 83	16	11.5	13.9				45	36	41 0	—	—	—	—	—	—	—	—	—	
II. Values for healthy aged persons																								
1. Newman & Gitlow (13)	65–104	M. 50	5.09	3.30	4.42	15	9.7	12 65	1.8	0.14	0 53	52 2	35	41.2	121	81.3	97 7	30 6	26 5	28.5	35.4	24 5	29.6	Sahli
		F. 50	5 21	3.20	4 11	16	7 8	11 7	1 28	0 37	0 64	52	25	36.7	123	67.5	90	32 8	26 5	28 8	40.7	26.4	32.3	
2. Olbrich (14)	>60	M. 41 RBC 41 Hb 38 PCV & MCV	6.19	3.98	5 07	17.4	11 0	13.9	—	—	—	50	37	45.1	97 5	79.4	89 5	—	—	—	—	—	—	Haldane-Gower
		F 48 RBC 47 Hb 46 PCV & MCV	5 69	3 65	4.76	16 0	9 9	13 2	—	—	—	52	26	42 0	100 4	60 6	88 4	—	—	—	—	—	—	

3. Fowler, Stephens & Stump (15)	65-80	M. 73 F. 27	—	—	4 81 4.46	16 0	9 7	13 1 12 5	—	—	—	51	33	41.7 40.4	—	—	—	—	—	—	—	—	—	Newcomer or Haden-Hauser
4 Miller (16)	60-104	M 100	5 5	3 5	4.46	17 5	12 0	14 3																Hellige
5 Bing (17)	>60	M 22 F. 21	9 8 9 4	4 9 4 2	5.1 5 1	120% 115%	88% 84%	101% 96%	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Not given
6 Hansen (18)	63-95	M 20 F 20	6 3 3 8	4 2 3 9	5 1 5 0	13 2 13 8	10 4 10 4	13 0 12 4	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	Sahli
7. Millet & Balle-Helaers (19)	57-85	M. 33 F. 41	5 32 5 02	2 32 2 84	3 93 3.96	120% 117%	57% 70%	93 1% 93 1%	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	Sahli
8. Rud (20)	63-90	M 7 F 8	5 50 5 37	4 40 4 28	5 10 4 68	108% 94%	86% 82%	100% 89%	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	Autenrieth & Koenigsberger Colorimeter
9. Williamson (21)	61-76+	M. 81 F 71	— —	— —	— —	— —	— —	15 82 15.39	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	Spectrophotometric
10. Ventura (22)	63-91	M. 20 F 20	5 12 6 97	4 37 3 65	5 04 4 90	102% 110%	80% 71%	88 5% 91 9%	1 08 1 61	0 14 0 15	0 57 0 82	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	Sahli
11. Puxeddu (23)	60-90	M 55 F 39	6 10 6 00	4 00 4 00	5 37 4.83	— —	— —	— —	— —	— —	— —	50 50	40 40	43 8 43 1	— —	— —	— —	— —	— —	— —	— —	— —	— —	
12. Dotti (24)	60-93	M 38 F. 33	6 46 5 26	4 39 4 07	5 16 4 59	109% 95%	70% 76%	93% 83%	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	— —	
13. Shapleigh, Mayes & Moore	60-95	M 50 F 50	5 98 5 55	3 72 3 83	4 75 4 71	17 2 16 2	10 9 11 6	14 1 13 7	4 2 3 8	0 2 0 4	2 01 1 66	51 46	34 35	42 1 40 8	110 101	74 76	89 2 87 3	33 64	24 15	29 8 29 2	36 25	27 30	33 5 33 5	Evelyn Colorimeter Oxyhemoglobin
Mean values		M F		(577) (358)	4 73 4 58	M (475) F (265)		14 69 13 47			M F	(266) (212)		43 69 40 46										

* In the column under "sex and no. of cases" the figures refer to the number of subjects on whom each determination was made. Hemoglobin values are recorded in grams per 100 cc except where "%" is indicated. In the mean values at the bottom of the table, the figures in parentheses indicate the number of subjects included in the calculation of mean values. For calculation of mean hemoglobin, only values reported in grams were used.

any value more than a few per cent less than normal should be investigated. The remaining studies (17, 21–24), on the other hand, showed no significant change in the number of red cells or the amount of hemoglobin as compared with younger age groups. In addition, Sjöstrand (25) determined the total amount of hemoglobin in the body of 266 adults; only a few of his subjects were above the age of 50, but the total hemoglobin seemed to remain constant throughout adult life. The mean value was calculated for all the red cell counts in table 1 and for all of the hemoglobin levels reported in grams per 100 cc. These mean values differ from those given by Wintrobe and Osgood for healthy young adults in two ways: they are slightly lower, and they show less difference between the two sexes.

There are fewer data for the packed red cell volume (table 1). The average mean values, however, are slightly lower than those recorded for younger age groups. Corpuscular constants were calculated by only three groups of investigators. Newman and Gitlow's figures (13) for mean corpuscular volume were slightly above, and those for mean corpuscular hemoglobin concentration slightly below usually accepted normal values. Our figures were within the normal range. Olbrich (14) and Millet and Balle-Helaers (19) described a definite increase in mean cell diameter, whereas Fowler, Stephens, and Stump (15) stated that there was no change. The reticulocyte levels reported in three studies show no significant deviation; the counts obtained by us are slightly higher than those reported by Newman and Gitlow (13) and by Ventura (22). This difference is probably of no significance since wet rather than fixed reticulocyte preparations were used and counts are usually somewhat higher with this technique.

In order to determine whether there was any further tendency for erythrocyte values to change with advancing age, the data collected by the authors on their 100 subjects were plotted on a scatter diagram (fig. 2). The graphs demonstrate clearly that there is no consistent rise or fall in the red cell, hemoglobin, hematocrit, or reticulocyte values in the age range of 60 to 95 years. These figures have also been submitted to statistical analysis for determination of the standard deviation. The results are summarized in table 2.

Little mention is made in the literature of qualitative changes in the erythrocytes of aged people. Anisocytosis, poikilocytosis, and polychromasia are apparently not found to any degree; this was true also in the [illegible] smotic fragility of the red cells [illegible] (14), but is normal according [illegible] f interest to know whether the relatively sedentary life of the aged causes red cells to have less trauma in circulation and leads to a longer life span of the corpuscles. The literature, however, contains no such information. Loge and Shapleigh (26),

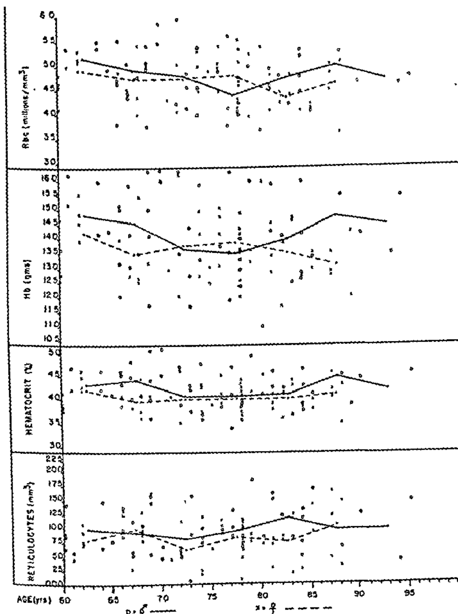


FIG. 2. Scatter diagram of erythrocyte, hemoglobin, hematocrit and reticulocyte values in 100 healthy old people.

using the technique of differential agglutination, have measured the survival of red cells from healthy young adults after transfusion into five recipients, 72 to 83 years of age. Fifty per cent of the transfused cells survived for 64 to 73 days; the total survival time varied from 128 to 145 days with an average of 136 days. No conclusions can be drawn from these five observations, but the results do suggest that red cell survival time in elderly people may be slightly greater than in young adults.

TABLE 2

Mean values for 100 healthy old people studied by the authors*

Sex	Age	RBC	Hb	Hematocrit	WBC	Platelets
		millions	*gm*	%	*mm³*	*mm³*
50 Males	60–94	4.75 ±0 57	14.1 ±1.53	42.1 ±3.98	7,730 ±2,170	732,000 ±299,000
50 Females	60–90	4.71 ±0 46	13.7 ±1 07	40.8 ±2.89	6,497 ±1,490	781,000 ±331,000

* And standard deviations.

Information about the red blood cell in subjects 60 or more years of age may be summarized as follows: there seems to be a slight but significant decrease in the erythrocyte, hemoglobin, and packed red cell values from levels found in healthy young adults. The decrease is probably more pronounced for men than for women so that the sex difference becomes smaller. The over-all mean values for data included in table 1 are:

	RBC	Hb.	Packed cell volume
	millions/mm³	*gm Hb /100 cc*	%
Men.	4.73	14 09	43.69
Women	4 58	13.47	40 46

Reticulocyte counts are unchanged. There is no further consistent tendency for any of these values to increase or decrease as age advances. The corpuscular constants are probably not altered, although the mean corpuscular hemoglobin concentration may possibly be a little lower. Qualitative changes in the erythrocyte are minimal if they occur at all.

LEUKOCYTE VALUES

The principal studies reported in the literature on the total number and distribution of white blood cells in the aged are summarized in table 3. Included again for comparison are the values proposed as normal by Wintrobe (11) and Osgood (12). Minimum and maximum levels for the total number of white cells extend over the wide range of 2,000 to 16,000 cells per mm³. In the authors' series of 100 cases the means and the standard deviations were: 7,730 ± 2,170 cells per mm³ for males and 6,497 ±

1,490 for females (table 2). The averages of all figures were 7,145 cells per mm^3 for men and 6,982 cells per mm^3 for women. There is, therefore, no significant deviation from the levels found in healthy young adults.

The differential leukocyte counts likewise show no consistent change from the normal. In five studies (14, 15, 27, 28, 30), the mean values for segmented neutrophils were higher than those given by Wintrobe and Osgood. Dotti (24), on the other hand, reported an increase in lymphocytes with a decrease in neutrophils and monocytes. The higher monocyte levels found by the authors may be explained by the fact that differential counts were made on supravital preparations which frequently yield higher percentages of monocytes than are usually reported on fixed, Wright-stained films. There also appeared to be a tendency to eosinophilia in the authors' series. Fifty-six per cent of the male subjects and 58% of the females showed 4% or more eosinophiles on the differential count. This might possibly be explained as a manifestation secondary to the atrophic skin changes commonly seen in the aged.

Figure 3 is a scatter diagram of the total white blood cells, polymorphonuclear neutrophils, lymphocytes, and monocytes per mm^3 in the 100 subjects studied, plotted against age. No significant increase or decrease occurred in these cells with advancing age.

No constant morphologic alterations have been observed in the leukocytes of elderly people. Olbrich (14), however, described increased lobulation of the nuclei of neutrophils with a concomitant decrease in granulation. Dobrovici (30) also believed that, in general, the cells are more mature The remaining investigators regarded leukocytes as being morphologically normal. In the 100 subjects studied by the authors, there were no changes noted and no increase in lobulation of the neutrophils.

Factors Related to Hemostasis

Almost no data are available concerning the hemostatic mechanism in the aged. Puxeddu (23) found the total platelet counts decreased in 94 subjects 60 to 90 years of age. Using 200,000 to 300,000/mm^3 as normal, he obtained a maximum of 198,680/mm^3 in males with a minimum of 54,893/mm^3. In females, the maximum was 175,600/mm^3 and the minimum 70,266/mm^3. Our results are not in agreement with this observation. Table 4 shows that the 100 subjects investigated by the authors had platelet counts well within, and in many cases above, the normal values for the method used (Dameshek, 400,000–800,000 per mm^3). Only a few subjects were found to have counts below the accepted normal minimum.

No studies made on people of advanced age have recorded bleeding times, clotting times, prothrombin levels or determinations of other components of the hemostatic mechanism. However, there is no evidence that

TABLE 3

Leukocyte values

Author	Age range	Sex & no. of cases	Total WBC (mm³) Max.	Min.	Mean	Bas.	Eos.	Myel.	Meta Myel	Stabs.	Segs.	Lymphs.	Monos	Comments
						%	%	%	%	%	%	%	%	
I. Normal values in young adults 1. Wintrobe (11)	Young adults	M. and F.	10,000	5000	7000	0–0.75	1–3	0	—	3–5	54–62	25–33	3–7	
2. Osgood (12)	14–30+	M. and F. *	11,500	4500	7400	0–2 Mean 0.5	0–8 Mean 1.9	—	—	0–5 Mean 0.8	33–78 Mean 54	15–65 Mean 38	0–9 Mean 4	
II. Normal values in aged 1. Olbrich (14)	61–89	M. 41	9000	4600	7020	0.0–3.0 Mean 0.5	0.0–7.0 Mean 2.3	0	—	0.0–1.0 Mean 0.64	Mean 71.8	10–46 Mean 22.9	0–8 Mean 2.3	Tendency to increased lobulation and decreased granulation of WBC. No total segmented form values given; divided into number of lobes
		F. 43	12,800	3200	7058	0.0–4.0 Mean 0.6	0.0–8.0 Mean 1.9	0–1	—	0.0–1.0 Mean 0.1	Mean 67.8	12–43 Mean 27.0	0–8.6 Mean 1.8	
2. Etienne & Pertin (27)	60–96	M. 20	12,800	5600	8680	1–2.5	1–2.5 Mean 1.73	—	—	—	57–74 Mean 67.1	18–36 Mean 24.85	1–8.5 Mean 5.1	Morphology normal essentially. No sex differenre in differential
		F. 7	9,200	5600	7371									
3. Newman & Gitlow (28)	65–104	M. 50	12,050	3000	8330	†0.3–1.0	†0.6–3.5	—	†0–0.3	Mean 5.1	Mean 60.2	Mean 33.5	†0.7–2.0	†Range of averages of 5 yr. age increments from 65 thru 94 yrs.
		F. 50	11,100	5050	8170	0.0–0.5	1.0–2.0	—	0–1.0	Mean 4.2	Mean 63.0	Mean 33.8	1.0–2.1	
4. Miller (15)	60–104	M. 160 F. none	13,000	4000	7700	0–2.0 Mean 0.7	0–8.0 Mean 2.7	—	—	—	40–75 Mean 57.5	15–50 Mean 30	1–15 Mean 7.8	WBC essentially the same as in younger age group

5. Gabbert, Hutaff & Harrell (29)	>70	—	16,000	2000	—	—	—	—	—	—	—	—	—	Total WBC same in aged as in young adults
6. Fowler, Stephens & Stump (15)	65–80	M. 73 F. 27	12,450	2900	7220	0–3 Mean <1	0–10 Mean 2.8	—	—	1–13 Mean 4	43–79 Mean 60 2	11–48 Mean 27.5	1–15 Mean 5 4	Total WBC and differential normal
7. Dobrovici (30)	67–81	M. 11 F. none	—	—	—	—	1.0–1 5 Mean 1 2	—	—	—	64 5–80.5 Mean 73	13.5–30 0 Mean 20 4	3–9 5 Mean 5.4	Tendency to more mature cells in aged
8. Dotti (24)	60–92	M. 26	8602	4948	7039	0–3 5 Mean 0 8	2 2–17 Mean 4 6	—	—	—	30 5–67.4 Mean 52 4	21–55 Mean 37.9	1–9 5 Mean 3 3	Total WBC normal with increase in lymphocytes, decrease in monocytes & segmented forms
		F. 35	7450	4000	5795	0–1.5 Mean 0 3	0.5–5 Mean 2.2	—	—	—	28.3–70 5 Mean 55 6	22–54 4 Mean 36.7	2 6–8.3 Mean 5 2	
9. Shapleigh, Mayes & Moore	60–95	M. 50	16,000	4250	7730	0–4 Mean 1.1	0–9 Mean 4 4	0–1	0–1	0–5 Mean 1.4	28–86 Mean 59.1	4–46 Mean 23.5	4–28 Mean 10.4	Morphology normal
		F. 50	10,350	3150	6497	0–3.0 Mean 1.0	0–17 Mean 4.7	0–2	0–1	0–8 Mean 1.5	28–75 Mean 55 6	11–62 Mean 27.7	2–19 Mean 9.1	
Average values		M. F.			(347)7145 (190)9526									

* Variable number—never less than 236.

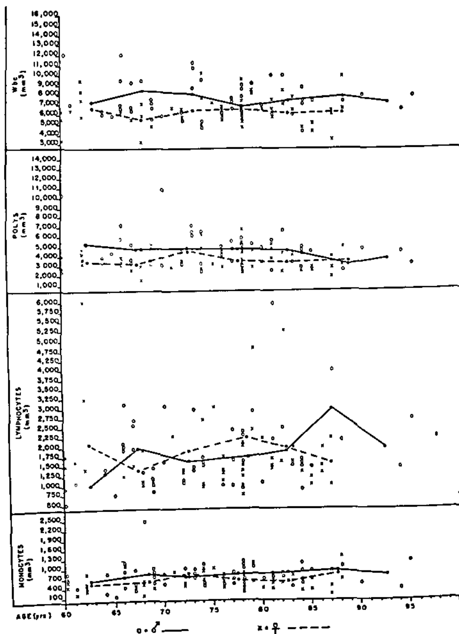


Fig. 3. Scatter diagram of total leukocyte, polymorphonuclear neutrophil, lymphocyte and monocyte values in 100 healthy old people.

hemorrhagic disorders, when seen in old persons, are related directly to the process of ageing. The only exception to this might be the so-called senile purpura which is due to an increase in vascular fragility secondary to the atrophic changes that occur in the skin and subcutaneous tissues with age.

SEDIMENTATION RATE

The erythrocyte sedimentation rate is widely used as a non-specific test which helps to establish the presence or absence of organic disease. It is important, therefore, to know if the sedimentation rate increases with

TABLE 4

Total platelet counts (per mm³) in 100 healthy aged subjects

Sex	Total cases	No showing < 400,000/mm³	No showing 400,000–800,000/mm³	No showing > 800,000 mm³
Male	50	10	21	19
Female	50	6	24	20
		Maximum per mm³	Minimum per mm³	Mean per mm³
Male	50	1,392,000	255,000	732,000
Female	50	1,430,000	330,000	781,000

TABLE 5

Sedimentation rates (mm. per hr.) in 100 healthy aged subjects

Sex	Total cases	No. showing 0–10	No showing 11–20	No showing 21–30	No showing 31–40	No showing > 40
Male	50	4	13	13	11	9
Female	50	3	5	12	14	16

advancing age in the absence of any pathologic changes other than those associated with the ageing process. Miller (31) studied the sedimentation rate of 389 male subjects over 60 years of age. Using a 10 per cent drop in 60 minutes as the upper limit of normal, he found that 245 (63 per cent) of his subjects fell within the normal range, 80 (20 per cent) showed a fall of 11 to 20 per cent, and the remaining 64 had rates that varied from

crease in the sedimentation rate with advancing age. His values varied from 2 to 37 mm. per hour for males and from 2 to 27 mm. for females; average rates were 12.1 and 11.7, respectively. The results obtained by the authors on their 100 subjects are summarized in table 5. The normal

limits used for the Wintrobe method after correction for hematocrit were: less than 10 mm./hr. for males and less than 20 mm./hr. for females. For only four of the men and eight of the women did the values fall within this range. Twenty of the men (40 per cent) and thirty of the women (60 per cent) had rates faster than 30 mm./hr. The data on the sedimentation rate in people of advanced age, therefore, are conflicting. Any conclusions must be postponed until further information is available.

The review made in this chapter emphasizes the incomplete and inadequate state of our knowledge about the hematologic system in the aged. About the only statement one can make with assurance is that the peripheral blood and bone marrow do not change strikingly as people grow older. The total volume of red, hematopoietically active marrow probably decreases, but the amount which remains is able to maintain erythrocyte values at levels only slightly lower than those found in young adults. Counts in men remain slightly higher than in women, but sexual difference in the average values becomes less. No consistent change has been found in the total number of white blood cells, the per cent of the several types of leukocytes, or the platelet count. Even these generalizations, however, are based on meager data and may need revision after more extensive studies have been completed.

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13

ARTERIOSCLEROSIS

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Scarcely a note in the recent literature on arteriosclerosis can be found which does not begin with a statement of the increasing importance of the disease. Disease of the arteries, as is well known, kills more adult persons in our society than any other disease. What may be considered even more important is the fact that it is also responsible for more disability than any disease except mental illness and perhaps the rheumatic diseases. A certain proportion of mental illness is, furthermore, generally considered due to disease of the cerebral arteries.

In view of recent comprehensive reviews on the subject of arteriosclerosis (1, 2, 3), there need not be an attempt here to describe in detail either the many factors to which its development has been attributed, or the lesion itself.

The term arteriosclerosis seems always to need definition. Although there may well be several processes contributing to the development of hardening of the arteries, to make the definition as simple as possible it might be said that what is here meant by arteriosclerosis is that lesion or combination of lesions which is to be found, to at least a minor degree, in the aorta and other major arteries of nearly everyone over 20 years of age (4).

To be sure, there is disagreement as to whether this complex comprises more than a single disease process (5). Recent evidence from the autopsy records from a London Hospital suggests that death from coronary disease has been increasing, while death from coronary arteriosclerosis was decreasing (6). If this fact is not due to passing fancies in diagnosis, it would suggest that the type of disease responsible for myocardial infarction differed fundamentally from the commonly seen coronary sclerosis. Medial calcification with hyperplastic fibrosis occurs sometimes independently of

atherosclerosis. When calcification occurs alone or almost alone and is confined for the most part to the muscular arteries, the condition is often called "Monckeberg's arteriosclerosis".

There is now general agreement that fibrosis and calcification in arteriosclerosis follow the introduction of lipid into the wall whether the lipid arrives by imbibition (7) or is carried in by wandering phagocytic cells (foam cells) (8) or remains as the remnant of blood extravasated into the wall of the artery from ruptured vasa vasorum (9). Evidence exists also to the effect that diffuse deposition of calcium in the wall with subtle changes in the elastic lamellae precedes and may, so to speak, prepare the wall for the deposition of the lipid elements (10). There is also the view that stress due to normal arterial pressure and shearing forces is a major factor in development of arteriosclerosis (2).

Arteriosclerosis has, in the past, been considered to be so closely associated with age, that many persons have taken for granted that it is part of the ageing process. This line of thought leads to acceptance of the disease as inevitable but numerous observations suggest that this is not the case. For one thing, arteriosclerosis does occur in young persons. In fact, there is evidence that when the lesions are diligently sought, some can be found in nearly every individual after the age of 7 years (11). For another, persons dying in the ninth and tenth decade often exhibit less arteriosclerosis than apparently normal individuals 50 or more years old (12). Groddeck found that one-third of persons over 80 years of age have minimal amounts of arteriosclerosis (13). One can argue that those who have arteriosclerosis die earlier and hence those who survive this period comprise the individuals who did not develop severe arteriosclerosis, but this argument is tenuous.

Pathology

Definition of arteriosclerosis in the present state of knowledge is possible only in terms of descriptive pathology. The following brief account is designed to make clear what sort of disease is under discussion.

1. *Atherosclerosis* consists of the deposition of material containing lipid in the intima or subendothelial region of the arterial wall either in cells as fatty droplets or free in the interstitial spaces. Fibrous thickening of the intima then takes place, followed by extension of the atheroma into the media with disruption of the elastic lamella and eventual necrosis of tissue.

2. *Arteriosclerosis.* Besides the lesions described under atherosclerosis, arteriosclerosis is taken to include additional morphological changes, such as the laying down of connective tissue about the fatty plaque and in the surrounding regions. Indeed, fibrous plaques with very little lipid present are seen, but it is not known whether these plaques represent ones from

which lipid has disappeared or ones in which lipid was not deposited. Necrosis and degeneration of subendothelial layers, elastic tissue and media occur, often with mild infiltration of monocytic cells. Calcium is laid down at the site of lipid deposition and especially at the site of degeneration. Frequently, where necrosis is marked, hemorrhage into the neighboring tissue occurs, the bases of the calcific fatty plaques are loosened, the edges come free, and ulcerate through the intimal lining. Occlusion of the lumen may occur as the result of thrombus formation over such an ulcerated area. Frequently, also, intimal proliferation and the underlying plaque may attain such size that the lumen is occluded.

3. *Medial calcification* (Monckeberg's sclerosis) is often classified or associated with arteriosclerosis. The differences are chiefly that there is little or no evidence of atheromatosis, that the lesion is confined to the media of arteries with well developed muscular coats, and that the aorta escapes damage. There may, however, be extension of the calcification toward the intima with intimal thickening, disruption of the elastic lamellae and scarring. This type resembles to a marked degree that which follows prolonged administration of high doses of vitamin D, adrenalin, and a number of other agents (1) and is, at least in pure form, uncommon.

To sum up, then, the combination of atherosclerosis with scarring and calcification is the common disease, "intimal sclerosis," (14) with which this discussion is concerned and does not include the medial sclerosis generally referred to as "Monckeberg's sclerosis."

Factors Influencing the Development of Arteriosclerosis

1. There is some evidence that *heredity* plays a part in the development of the disease but it is far from clear what part heredity plays and what part is due to common habits and environment (15). Coronary thrombosis seems to be much less frequent in Chinese than in the people of the United States (16) but Chinese in this country appear to be subject to the disease more commonly than their fellow countrymen in China. There is also evidence that occurence of coronary sclerosis may be a genetic dominant trait (17).

2. Certain *anatomical and physiological developments* which in point of time precede the development of arteriosclerosis might be thought of as preparing the arterial wall for the disease, for example, the redundancy of the intima of the coronary arteries described by Dock which is present at birth and is much more marked in the male than in the female (18). Such an anatomic arrangement might encourage the development of arteriosclerosis and might help explain the difference in incidence of coronary disease between the sexes.

The bearing of biochemical and histological changes in the arterial wall,

which have been shown by Lansing and associates (19) to begin between the ages of 15 and 25 years, must be considered in relation to subsequent events. It appears that the elastic tissue of both elastic and muscular arteries undergo age changes typified by an increased affinity for calcium (Fig. 1). Regional variations in the age changes of arterial elastic tissue imply a significant relation between alterations in the wall of the artery and atheromatosis. In this regard it is worthy of note that the pulmonary artery is resistant to calcific age changes in its elastic tissue. Amino acid analyses

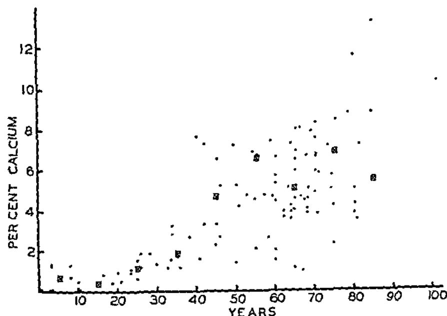


FIG. 1. Graph showing analytical data for calcium content of elastin with age. Calculated on basis of dry weight of elastin.

of arterial elastic tissue indicate an increase with age in the contents of aspartic and glutamic acids, the dicarboxylic amino acids. The free carboxyl groups in these amino acids may account for the affinity for calcium of old elastic tissue. Perhaps these changes are the chemical counterpart of the changes in physical behavior—namely, loss of elasticity or increase in rigidity which have previously been described (20, 21). The changes in elasticity take place in the absence of arteriosclerosis and advance with age.

3. The role of *stress and strain* has been shown in many ways to be of great importance in the development of the disease. Few assign stress or tension the primary role but the evidence is ample that once the conditions

for development of arteriosclerosis have been laid down, stress and tension play a large part. There is the fact that the pulmonary arteries are almost never the site of extensive arteriosclerosis unless pulmonary hypertension exists. This fact would make it appear that normal arterial tension may favor the development of arteriosclerosis and hypertension is associated with even greater frequency and amount. The appearance of arteriosclerosis in the arteries of the legs where hydrostatic pressure is added to the arterial pressure, earlier and more frequently than in the arteries of the arms, yields additional evidence. Wilens' enlightening experiments in rabbits strengthens this view greatly (22). In cholesterol-fed rabbits he was able to alter the site of development of the most marked lesions depending upon the position in which the rabbits were maintained during the feeding period.

Besides simple arterial pressure shearing stresses also appear to play a role. Wherever arteries are tightly fixed, sclerosis is more apt to occur, for example, on the posterior aortic wall near the mouths of the intercostal arteries and at the division of the aorta into the femoral vessels. An excellent discussion of this point is to be found in Gubner and Ungerleider's recent review (2).

4. Winternitz believed that *necrosis with rupture of the walls of vasa vasorum* and hemorrhage into the arterial wall played a large role in initiating the lesion (9). The inference was that other more soluble and diffusible substances of the blood were removed and cholesterol was left behind. Recent knowledge concerning the high degree of metabolic activity of cholesterol (23, 24, 25) would tend to make this thesis unlikely.

5. Evidence linking the *metabolism of the lipids*, chiefly cholesterol and the phospholipids, with the development of atherosclerosis and arteriosclerosis is strong. Analysis of clinical data and recent experimental work have indicated that the manner in which the body handles lipids is of great importance in the development of the disease. Just how important, in what way, and which of the group of lipids and lipoproteins plays the greatest role are yet to be learned, but recent original work in several fields has made possible new lines of investigation of this particular problem. The evidence for a relationship between disturbances in lipid metabolism and the disease arteriosclerosis stems mainly from two sources: 1) the production of diseases in animals similar to arteriosclerosis in the human by raising cholesterol levels of the plasma, and 2) the association of human arteriosclerosis with diseases in which hypercholesterolemia is a common factor. Attempts to produce arteriosclerosis in animals have met with success in the presence of high serum cholesterol levels associated with feeding cholesterol. This type of study began with Ignatowski (26) and with Anitschkow's work in rabbits (8). The results have been confirmed many times in rabbits and extended to include chickens, among the ani-

mals which develop atherosclerosis when fed cholesterol (27). Certain factors, such as the thyroid hormone and iodides (28), have been shown to influence to some degree the rate at which atherosclerosis develops.

An interesting development in experimental arteriosclerosis in animals arose from Dragstedt's observation that dogs made diabetic by total pancreatectomy developed arteriosclerosis of a mild degree roughly 3 times more frequently and to a considerably greater degree than did normal dogs. He observed also that feeding fresh pancreas and perhaps pancreatic extract to diabetic dogs tends to inhibit the development of arteriosclerosis. In this connection Duff and McMillan observed that alloxan diabetes of rabbits was not only not accompanied by atherosclerosis but that its presence inhibited the development of atheroma although there was marked elevation of serum cholesterol levels (3).

Recently, taking advantage of the action of antithyroid drugs in combination with cholesterol feeding, Steiner, Kendall and Bevans have been able to produce arterial lesions in dogs. This goes far toward bridging the gap between *atherosclerosis* in an herbivorous animal (the rabbit) and arteriosclerosis in an omnivorous one (man) (30). The lesions in the dog involve the coronary, cerebral and other vessels as well as the aorta and go well beyond the simple deposition of cholesterol either within or without the cells of the intima. Fibrosis, hyalinization, disruption of elastic tissue, degeneration with hemorrhage into tissue and calcification are seen within the plaques. Thus the similarity to human arteriosclerosis is impressive.

The other source of evidence is a long list of clinical material associating human arteriosclerosis with conditions known to exhibit hypercholesterolemia, i.e., xanthomatosis, myxedema, diabetes mellitus, and nephrosis. It has also been shown that, in persons with coronary thrombosis, blood cholesterol levels are higher and more variable than in persons without evidence of the disease. Ungerleider has observed that in a large group of individuals whose blood cholesterol levels were moderately increased and in an equally large group whose levels fell within the normal range, evidence of arteriosclerosis appeared with about equal frequency (2). However, a group whose levels could be considered at the lower limit of the normal range exhibited much less arteriosclerosis. The observation contains the suggestion that there may be a critical level below which arteriosclerosis is less likely to occur. The observation that the Chinese whose plasma cholesterol levels are lower than ours are less prone to arteriosclerosis bears some weight. Some evidence is suggestive of the fact that in areas where, or at times when, food is short, incidence of coronary thrombosis is less frequent (32). Studies in Norway of the period of privation during the last war set forth similar observations (33). All of this evidence is circumstantial. It suggests that in some way, blood lipid levels

influence the deposition of cholesterol in the arterial wall. It must, however, be kept in mind that for the most part human arteriosclerosis develops in the absence of the high levels which appear necessary for the production of the disease in animals.

Clearly, other factors play a role. Several investigators have observed that the ratio of phospholipids to cholesterol in the plasma may be a modifying factor in the development of atherosclerosis. Kellner has shown that the blood cholesterol levels of rabbits can be markedly elevated by injecting one of the surface acting agents (Tween-80 or Triton) (34). Under these circumstances the phospholipids rise to a greater degree than does cholesterol and atherosclerosis is much less readily produced. Likewise, in alloxan diabetes in rabbits with marked lipemia in which atherosclerosis fails to develop, the phospholipids are also markedly elevated (3). It has also been suggested that in biliary cirrhosis with xanthomatosis where the phospholipids are elevated to a greater degree than is cholesterol and the plasma remains clear there is no increased incidence of arteriosclerosis (35).

Pomeranze and Kunkel (36) in a thorough study of a large group of diabetics, have shown that the phospholipid-cholesterol ratio served well to divide those individuals who exhibited evidence of arteriosclerosis from those who did not. Almost all of those whose ratio was less than 0.89 exhibited evidence of arteriosclerosis.

Striking advances in knowledge concerning lipid metabolism have recently come from two quite distinct lines of investigation. Both have a direct bearing on the relationship between arteriosclerosis and the manner in which the body handles lipids. One, the fractionation of blood serum by chemical and physical means has shown that the phospholipids and cholesterol are present in blood plasma as large molecules in combination with protein (lipoproteins) (37, 38). Two, the ability to label cholesterol and some of its metabolic building stones (as acetate) with various isotopic elements has permitted studies which demonstrate that cholesterol is metabolically an intensely active substance (23, 24, 25).

Gofman has studied the lipoproteins in individual sera by an ingenious use of the ultracentrifuge (39, 40). By use of a proper concentration of salt, he has made certain of these components move centripetally. He [illegible] -8 (S_f is the Svedberg sedimen- [illegible] are found in all normal sera and [illegible] interesting is the fact that in many sera he finds faster moving macromolecules. He has studied intensively those moving at a rate of S_f10–20 although there are whole families of larger macromolecules which move still faster than these. As the molecules grow larger they appear to contain a higher proportion of neutral fat.

The group of molecules on which his attention has been centered he finds more commonly in men than in women and more commonly in groups of individuals suffering from coronary thrombosis. The correlation between the presence of these molecules and coronary thrombosis is good but that between these molecules and cholesterol levels of the plasma is poor. Keys has, however, (41), by detailed statistical analysis, shown with Gofman's figures that correlation of the occurrence of coronary thrombosis is just as good and perhaps better with total cholesterol levels of the blood than with the number of the abnormal lipoprotein molecules which Gofman measured. When patients were placed on a low cholesterol low fat diet, the S_f10–20 class molecules tended to disappear.

Striking, too, is the evidence of the appearance of these molecules when atheroma of the aorta appear in cholesterol fed rabbits. It has also been observed that this class of macromolecules are to be found in the serum of dogs in which arteriosclerosis was present as a result of feeding cholesterol and thiouracil (42). What the association of these large lipoprotein molecules with arteriosclerosis means is yet to be learned. From the present evidence it would be difficult to say whether they play a protective role or an active one in the development of atherosclerosis.

By chemical methods of fractionating plasma (37, 38) Barr, too, has studied the lipoproteins of normal and arteriosclerotic subjects with rewarding results (43, 44). He has found that the alpha lipoproteins tended to be higher in patients who exhibited unequivocal evidence of the presence of arteriosclerosis than in groups of comparable age and sex who did not exhibit such evidence. It seems likely to him that Gofmans' S_f10-20 molecules might be a part of the larger group of beta lipoproteins measured by the chemical separation. Changes of the same nature were extreme in nephrosis and were also exhibited to a moderate degree in diabetes. Of considerable interest is the fact that in the group of normal young women, (18 to 35 years) the value of the alpha lipoproteins was higher than in any group studied including the group of normal young men (18 to 35 years). It is, of course, just this group of individuals that is least liable to suffer coronary occlusion.

It is also of interest that the difference between men and women disappeared in the older age groups (40 to 65 years).

Pomeranze and Kunkel have demonstrated that the preponderant lipoprotein in hyperlipemic diabetes is a very different one from that in biliary cirrhosis (36). In diabetes the increase appears to be associated with the β lipoprotein fraction while in biliary cirrhosis, the increase is in the α lipoprotein fraction. Thus a whole field of investigation is opened up for studying the relative importance of a wide variety of macromolecular lipoproteins in the development of arterial disease.

The second imposing bit of knowledge obtained recently concerns the metabolism of cholesterol. Until a relatively short time ago, cholesterol was taken to be a relatively inert substance, metabolically speaking. Recently, the results of studies involving the use of radioactive acetate and radioactive cholesterol have shown it to be a very active metabolite, continually undergoing synthesis and degradation in the body tissues (23, 24, 25). The liver, adrenal, intestine and skin have the ability to synthesize cholesterol from acetate with great rapidity. This knowledge tends to diminish the importance assigned to dietary cholesterol.

Study of the relationship of lipid metabolism and transport, particularly that of cholesterol and phospholipids, to the deposition of lipid in the arteries is at the moment a very exciting venture. One can pursue the studies from many points of view—the importance of the phospholipids and their relation to cholesterol, the various forms of lipid protein complex, or the kinds of protein with which lipid can unite. Correlations of these various factors with the naturally occurring or spontaneous disease can and should be drawn. A great deal of work—in fact more work than was possible before the recent discoveries—must, however, be accomplished before the part played by any one factor becomes clear.

6. The part that local cellular mechanisms play in the development of arteriosclerosis has not received much direct attention. Loosening of the intercellular cement, for whatever reason, has been considered by many as a possible mechanism since the time of Virchow. This phenomenon might or might not be a function of the endothelial cells. Anoxia which gives rise to increased permeability might be more certainly considered an example of altered cellular metabolism as might the effect of thyroid in decreasing the permeability of the cells. Since atheromatosis is known to regress following cessation of cholesterol feeding, there are obviously normal cellular mechanisms present for disposal of lipids. It is possible that loss of ability to remove cholesterol might lead to its accumulation in the cell, an idea expressed by Leary (43). Lastly, the demonstration that the arterial wall can synthesize cholesterol from acetate *in vitro* (44) adds the possibility that rate of synthesis by the cells of the arteries involved might play a part. This finding emphasizes the importance of studying cellular mechanisms and should serve to stimulate investigation in this field.

Therapeutic Endeavors

As Clendening once remarked, the efficacy of a remedy for a disease is roughly inversely proportional to the number of remedies offered (45). Based on what is termed "lipotropic" action various agents, for example choline and inositol, have been suggested (46) as agents which might affect the deposition of fatty plaques in the arteries but there is considerable

evidence that they are ineffective (47). The thyroid hormone has also been used because of the effect it is known to exert on experimental arteriosclerosis in rabbits and some success is claimed.

Diets low in cholesterol and fat have been advocated on somewhat firmer grounds perhaps since it has been observed that such a diet will lower to some degree the level of cholesterol in individuals who have abnormally high levels to begin with (48) and in coronary disease the abnormal lipoproteins tend to disappear (40). What not to eat is, however, far from clear. There is some likelihood that as well as being low in cholesterol and fat, the diet must also be deficient in calories. Keys has shown that simple addition of vegetable oils to a cholesterol low diet will effect a return of serum cholesterol to previous levels (48) It must, however, be recalled that it is really not known whether these moderate reductions in cholesterol are of importance. Ungerleider's evidence suggests that very low levels of cholesterol must be reached to be effective. Also, the evidence that cholesterol is synthesized at a much lower rate when the diet is rich in cholesterol would tend to negate the value of withholding this substance from the diet (25). In conclusion, the rational therapy of arteriosclerosis, although perhaps not as far down the street in the light of present knowledge as it was ten years ago, is well around the corner.

Notions concerning the mechanisms of development of arteriosclerosis have changed greatly in the past few years. It is no longer considered the result of how long an individual has been alive. Predominant among present trends is the notion that difficulty in the handling of lipids by the body as a whole or by the cells of the arterial wall is one of the major factors in the development of the disease. It is clear, just as in lobar pneumonia or scarlet fever, that a concatenation of events is essential for the development of arteriosclerosis. Perhaps cholesterol levels must attain a certain value in the serum before severe arteriosclerosis can develop but, having reached this theoretical level, other events must occur simultaneously before extensive development can occur; the arterial pressure must be at such and such a level, or the ability of the intimal cells to take up cholesterol must increase or the ability of the cells to dispose of cholesterol must vanish. At least two or more of the factors that have been discussed may have to be present in order that the train of pathological events leading to arteriosclerosis can take place. It remains for the ingenuity of the investigator to assign a value to each factor and perhaps to discover other factors not now under consideration.

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14

EXPERIMENTAL HYPERTENSION

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The challenge presented to gerontology by the problem of hypertension is surpassed in magnitude by that of few other diseases. Goldblatt (71) recently stated, "... the death rate from arteriosclerotic disease of the brain, heart and kidneys, associated with the symptom of hypertension continues to be very high (about four times that of cancer)". The numerous advances in our knowledge concerning hypertension which have accrued during the last fifteen years bear witness not only to the paramount position occupied by this disease in clinical medicine, but also to the magnitude of the stimulus given investigators by the classical experiments of Goldblatt. Indeed, it is perhaps not an overstatement that most modern concepts of the nature of hypertension stem either directly or indirectly from his original demonstration that a permanent elevation in blood pressure could be produced by prolonged compression of the renal arteries (77). Since that time much has been learned concerning the importance of other factors such as the adrenal cortex, dietary composition and the role of the central nervous system. From these accumulated data a pattern now appears to be emerging. There is much to indicate that the development of hypertension is favored by those factors which tend to induce depression of certain aspects of renal function or overstimulation of the adrenal cortex. Conversely, factors which favor the maintenance of the normal metabolic state of the kidneys or which depress adrenal cortical secretion, seem to reduce the level of blood pressure in many hypertensive states. With this in mind, the relation of the kidney and the adrenal cortex to hypertension will be considered. From this it will be seen that many of the known effects of diet on the level of blood pressure can to some extent, at least, be explained by the effect on either the kidney, the adrenal cortex or both.

KIDNEYS

Constriction of the renal arteries of the dog produces hypertension characterized by hemodynamic alterations which correspond closely to those found in essential hypertension in man (75). This procedure is followed by a sustained elevation of blood pressure when applied to not only dogs, but also monkeys (67), rats (61, 170, 204, 210, 244), rabbits (197, 200), goats, sheep (74) and other species. Much of the available evidence indicates that man should also be included in this list Partial constriction of the aorta above the origin of the main renal arteries of dogs (73, 207, 234), or between the origin of the renal arteries in rats (with occlusion of the left ureter—the "endocrine kidney") (217), also results in hypertension

Permanent elevation of the blood pressure is now known to follow many other types of surgical manipulation of the kidneys; excision of two-thirds or more of the total renal mass in rats (24, 25, 26) and in dogs (155, 249, 250); wrapping the kidneys of rats in cellophane (44, 89, 182, 183), in cotton (34), cellulose acetate (252) or with rubber latex (1). The last procedure has also been applied successfully to rabbits (57). Application of plaster of Paris to one kidney to prevent hypertrophy after the other has been removed is followed by hypertension in the rat (91). A procedure which is widely used to produce elevation of the level of blood pressure in rats is that devised by Grollman (98) which consists of the application of a "figure-of-eight" ligature to the poles of either one or both kidneys. Renal arterial ligation followed by partial infarction of the kidney (153), or damage to one kidney produced by two to three hours of complete ischemia with subsequent removal of the other (146) are also followed by hypertension in rats.

Hypertension in experimental animals may accompany renal damage produced by non-surgical measures; these include injection of nephrotoxic sera (8, 157, 158, 159, 228, 229, 231), injection of broth cultures of hemolytic streptococci and streptococci viridans from urine of hypertensive patients (36), renal damage produced by oxalates (7) or by vitamin D in massive doses (6, 117, 123). The nephrotoxic effect of tyrosine in excessive amounts added to the diet (137, 151, 171, 236) is associated with hypertension (156, 212) which may appear within two weeks after the addition of the tyrosine supplement (235). Repeated injection of tyramine into rabbits causes renal arteriolar necrosis of the type associated with hypertension in man (43). The renal damage produced in young rats by a brief period of dietary deficiency of choline (94) is followed by hypertension (129) but this will be discussed more fully when considering the effects of dietary factors.

Unilateral renal hypertension

Goldblatt (68) found that compression of one renal artery of dogs did not result in a permanent hypertension unless the other kidney was removed. If unilateral nephrectomy was not performed, the hypertension was transient and removal of the affected kidney or release of the constriction at the height of the elevation of the level of blood pressure resulted in a prompt drop to normal (17, 69). In the rat and rabbit, however, unilateral renal damage produced by a variety of methods may result in a sustained hypertension (56, 61, 97, 176, 190, 246) which may persist even when the affected kidney is removed if the duration and severity of the hypertension has been sufficiently great (61, 190, 247). Grollman (100) found this to be true of the dog following ligation of the poles of one kidney, in contrast with the earlier investigations of Goldblatt in which the renal artery was constricted by means of his clamp. The persistence of hypertension under these conditions has been attributed to the development of structural damage induced in the remaining kidney by the hypertension *per se* (115, 116, 247), but more recently it has been reported that histological evidence of this cannot be consistently demonstrated (58), and it was stated that even the juxtaglomerular cells may appear normal. Grollman (97, 98, 106) has suggested that the prompt rise in blood pressure which follows the application of a Goldblatt clamp may be due to ischemic necrosis in portions of the affected kidney, and that the hypertension which persists after the removal of one damaged kidney in the rat, rabbit or dog in his experiments is due to reduction of the total amount of normal functioning renal tissue.

Theories to explain the hypertensive effect of renal damage

It is apparent from the foregoing that there are at least two possible explanations for the renal origin of hypertension. The first theory to be considered postulates the secretion of a pressor substance by the ischemic or damaged kidneys, a view which has been supported by Goldblatt (71), Page and Corcoran (186) and, in South America, Braun-Menendez and his group (17). A series of brilliant experiments devised by these investigators have established that the enzyme, renin (originally demonstrated by Tigerstedt and Bergman in 1898 (238)) from the damaged kidney enters the blood stream to act upon a substrate, hypertensinogen or renin-activator, a globulin in plasma, to form hypertensin or angiotonin, the active vasoconstrictor substance which can be inactivated by hypertensinase, an enzyme in the blood and in extracts of some organs. The renin-hypertensin theory is further supported by recent reports of the successful production of anti-renin and anti-hypertensin substances (14). Renin, however, has

only been demonstrated in significant amounts in the blood in the initial stages of experimental hypertension after which it falls to very low levels or disappears. Both animals and man exhibit the phenomenon of tachyphylaxis to renin and this is a potent argument against accepting the renin-hypertensin theory. Zweifach, Shorr, et al (226) have demonstrated the presence of a vaso-excitor material—VEM—in the renal veins of dogs made hypertensive by application of a Goldblatt clamp. The presence of VEM is masked by a corresponding increase in a vaso-depressor substance —VDM—during the chronic stages of hypertension. It is obvious however that the presence of the kidneys, damaged or otherwise, is necessary for the maintenance of the hypertensive state if the renin-hypertensin theory is adopted, or if it is accepted that the renal secretion of some substance such as VEM produces the elevation in the level of blood pressure. The evidence that hypertension may exist in the bilaterally nephrectomized animal will be considered below.

An alternative explanation for the renal origin of hypertension, which has recently received much support, postulates that abnormal elevation of blood pressure is *prevented* by normal renal tissue independently of its excretory functions. This view in one form or another has been proposed by Merrill, Williams and Harrison (165), and perhaps most vigorously by Grollman (101) who has provided much evidence in its favor by the results obtained from a series of well-designed experiments. Hypertension was found to persist for several hours following the removal of the remaining kidney from unilaterally nephrectomized dogs which had previously been rendered hypertensive by the application of a "figure-of-eight" ligature (100). In parabiotic rats, Grollman and Rule (108) found that the nephrectomized twin became hypertensive, while the blood pressure of that with intact kidneys remained within normal limits. Previously Braun-Menendez and Euler (16) had shown that 33 per cent of totally nephrectomized rats became definitely hypertensive, and so concluded that some completely extrarenal factor was of importance in maintaining the hypertension, although they did not stress the possibility of a normotensive function for kidneys

emphatic in stating that hypertension was always absent unless some renal tissue was present. With the advent of techniques for satisfactorily maintaining bilaterally nephrectomized dogs for several weeks by the use of the 'artificial kidney' and specially devised diets (169), the levels of blood pressure in such animals could be studied in the absence of complicating factors introduced by the development of uraemia and terminal morbidity. By this means it was established by Grollman and his associates that blood

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the importance of a reduction in renal pulse pressure after application of a Goldblatt clamp, but the evidence for this is not conclusive It is clear however that if the circulation to the affected kidney is restored by releasing the clamp or by establishing a collateral circulation by means of lieno-renal omentopexy (242), the hypertension is abolished. In the latter experiment it is of interest that the anastomoses so established were found to be *post-glomerular* in position. At the present time it seems that the bulk of the available evidence supports the view that the hypertensive effect of renal arterial constriction and other surgical procedures applied to the kidney, is the result of depression of some essential aspect of renal function, the exact nature of which remains to be determined The possibility that the juxtaglomerular complex may be responsible for this action of the kidney is supported by little evidence as yet, but will be considered in a later section.

Adrenal Cortex

It has long been recognized that the hypotension seen in Addison's disease is associated with adrenal cortical dysplasia. The opposite condition—adenomatous hyperplasia—has been reported by Rinehart et al. (203) as a frequent finding in hypertensive patients with vascular disease, but other investigators have not confirmed such a constant relationship (20, 35, 42). More recently Fisher and Hewer (55) found the steroids of the adrenal cortex increased to a significant degree in over 50 cases of essential hypertension. Perera and his associates (191, 192, 193, 194, 195) have reported that administration of desoxycorticosterone to hypertensive patients, who had developed Addison's disease with a fall in the levels of their blood pressures to normal or subnormal, restored the hypertension. DCA in similar amounts did not produce elevation of blood pressure in nor

or

sur

tion of the hormone. Thus hyperfunction of the adrenal cortex may play a role, at least under certain conditions, in the etiology of essential hypertension in man.

The importance of the role of the adrenal cortex in the experimental production of hypertension has been abundantly demonstrated. Hypertension cannot be produced in bilaterally adrenalectomized dogs by the application of Goldblatt-clamps, and removal of the adrenals from dogs previously rendered hypertensive by this means, promptly reduces the level of blood pressure to normal or below (53, 68, 181, 205). Hypophysectomy produces a slower and less dramatic reduction of blood pressure in Goldblatt-dogs, but this can be prevented by further constriction of the

clamp (72, 188, 189) or by the administration of either adrenocorticotropic hormone (5, 177), adrenal cortical extracts or desoxycorticosterone acetate (180). Conversely, in rats which have become hypertensive following renal arterial constriction, there is a very significant increase in the total mass of the adrenal cortices (179). Thus the action of the anterior hypophysis on the level of blood pressure appears to be exerted through the adrenal cortex and the latter is necessary for either the production or maintenance of the renal hypertensive state.

The response to injected renin (62, 184, 202, 237, 244) and the amount of circulating renin substrate (76, 136, 150) are reduced following the removal of the adrenals from Goldblatt-dogs, although there is no alteration in the sensitivity of the animals to the pressor action of hypertensin (136). Adrenalectomy also abolishes the formation of VEM in the cortex of the anaerobic kidney; this is restored by the injection of DCA (226, 227).

Adrenal cortical hyperfunction as represented by the injection of desoxycorticosterone produces hypertension in the domestic fowl (214) and the rat (220, 221). It has also been shown to have an immediate pressor effect in arterial hypertension (78, 79). In the rat, arterial pressure is increased, rate of renal blood flow decreased and filtration fraction elevated along with the ratio of sodium to chloride in the serum (2, 19, 66). Elevation in the ratio of serum sodium to serum chloride has also been found in hypertensive patients (213). The hypertensive effect of DCA is intensified by renal damage produced by a variety of means, including unilateral nephrectomy (64), nephritis due to nephrotoxic sera (144) and by dietary choline deficiency (2). This action of DCA is also heightened if the animals are rendered diabetic by removal of 95 per cent of the pancreas (18). The injection of DCA produces renal damage (214) which resembles that found in cases of malignant hypertension in man (222, 225). It has been suggested that the renal injury initiates the humoral mechanisms of the renin-hypertensin system (71) in rats injected with DCA. However it has now been established that hypertension and renal enlargement begin with the first injections of DCA (65) and the pressor effect of DCA is active in the absence of both kidneys. When DCA pellets are removed from otherwise intact rats, blood pressure returns to normal (66). These findings suggest that the normal kidney excretes or inactivates DCA (113). Progesterone when injected into rats, acts somewhat similarly to DCA (224) as does estradiol (2), whereas methyl testosterone has an inhibitory effect on the development of nephrosclerosis and hypertension due to DCA injection (223).

Castration of male rats accompanied by unilateral nephrectomy appears to sensitize the animals to injection of lyophilized anterior pituitary extract (LAP) so that hypertension results (112, 218). Adrenalectomy prevents

the development of this type of hypertension and abolishes it if it has first become established. The renal lesions produced are similar to those which result from the injection of DCA (114). For these reasons, the effect of the crude extract of anterior pituitary is believed to be mediated through the adrenal cortex by the liberation of hormones of the desoxycorticosterone type. Selye (215, 218) has shown that non-specific stress—particularly that produced by a cold environment—may stimulate the liberation of DCA or similar hormones from the adrenal cortex, and he suggests that such mechanisms may initiate the development of hypertension in man under certain conditions.

The effect of varying the intake of salt or protein in rats injected with DCA or with LAP, on the level of blood pressure is pronounced, but will be discussed under the heading of diet. From the data reviewed in this section, it seems clear that adrenalectomy or hypofunction of the adrenal cortex produces a fall in the level of blood pressure in both normal and hypertensive animals as well as man. The injection of hormones of the desoxycorticosterone type elevates blood pressure, at least in the presence of renal damage. The normotensive function of the intact kidney may well be the effect of renal inactivation or counteraction of these adrenal hormones by some mechanism which is essentially independent of excretory activity. It has not yet been reported if hypertension following bilateral nephrectomy can be abolished by adrenalectomy, and it will be readily apparent to the practical investigator that a falsely positive result might easily be obtained in this type of experiment. However if this should be clearly established to be the case, an analogy might be drawn between the normotensive, nephrectomised, adrenalectomized dog and the non-diabetic, depancreatectomized, hypophysectomized dog (Houssay).

Since this chapter was sent to press, a report appeared (Turner, L. B. and Grollman, Arthur; 1951. "Role of adrenal cortical activity in experimental hypertension induced by bilateral nephrectomy in the dog." Am. J. Physiol., 166, 185–190) in which evidence is presented that similar degrees of adrenal cortical stimulation (measured [illegible]

of the loss of renal tissue and not attributable to increased adrenal cortical activity.

Experimental Neurogenic Hypertension

It has been known for many years that a sustained elevation of blood pressure may sometimes follow section of the carotid sinus and aortic depressor nerves of rabbits (145). Results were not predictable however until the development of the excellent techniques of Heymans and Bouckaert (131, 133) and of Nowak and Walker (173). This type of hypertension in dogs is abolished by sympathectomy (9, 131) only if the sympa-

thetic denervation includes the kidneys and adrenals (96). This suggested that neurogenic hypertension might be essentially of renal origin due to excessive vasoconstrictor activity of the renal arterioles (95). However alteration of the renal histology in dogs with neurogenic hypertension has not been demonstrated consistently (50, 134, 135, 154, 172) although in both rabbits (80) and dogs (51), hyperplastic lesions of the renal arterioles have been reported. In dogs with neurogenic hypertension, a disproportionally small increase in the clearance of p-aminohippurate compared to that of creatinine has been taken to imply that the sites of increased renal vascular resistance were in the efferent glomerular arterioles (59). The haemodynamics of neurogenic hypertension differ from those found in experimental renal hypertension and in essential hypertension in man in that cardiac output is increased, renal blood flow remains the same owing to the renal arteriolar constriction, and blood flow through the limbs is increased due to lowered peripheral resistance (11).

Kaolin injected into the cysterna magna is followed by hypertension in dogs (37, 92, 130) and in rats (93), but not in cats (152). It is abolished in dogs by renal denervation (15) but persists in both the dog (138) and the rat (93) following bilateral adrenalectomy even when treatment with salt and adrenal cortical hormones is minimal. As parasympathectomy abolishes the acute rise in blood pressure in dogs which accompanies a sudden increase in intracranial pressure, sympathetic cardiac innervation may play an important role in the production of neurogenic hypertension (60). Prolonged stimulation of the plexus of nerves surrounding the renal arteries produces an elevation in the level of blood pressure which promptly returns to normal after the stimulation has been discontinued (147). This would indicate that if comparable nervous stimuli play any part in the etiology of hypertension in man, they must be continuously operating—at least for many years.

Hypertension has been induced in rats by exposing the animals to repeated loud noises (164) and this may be related to the neurogenic type since histological evidence of renal damage during the early stages of audiogenic hypertension is absent (52). This type of hypertension however differs from the neurogenic in that adrenalectomy lowers the blood pressure even if the auditory stress is continued although histologic changes in the adrenals could not be demonstrated (160, 251). An elevation in the blood pressure of rats has been reported to follow enucleation of both eyes (63) but the explanation of this has not been established beyond conjecture.

Since renin cannot be demonstrated in the blood of hypertensive animals or man in significant amounts except in the initial stages of the condition, it has been suggested that neurogenic factors may be responsible for the maintenance of the chronic phase of essential hypertension. This view has

received much support from Ogden (175) who has reviewed the evidence on which it is based, including the depressor effect of sympathectomy in hypertensive patients and of certain drugs which inhibit vasoconstriction due to nerve impulses.

Diet

Dietary treatment of essential hypertension in man by restricting the intake of salt, protein or calories, has been the subject of recent and excellent reviews by Pines and Perera (198) and by Chapman and Gibbons (28). Rigid limitation of the salt intake frequently appears to be of definite value in the treatment of the hypertensive patient (33, 40, 104). The rice diet advocated by Kempner (142, 143) is partly responsible for reviving the interest of clinicians in this form of therapy, but diets low in salt were employed for this purpose many years ago by Allen (3). Convincing experimental evidence for this clinical procedure was lacking until recently Some of the data concerning the effects of dietary protein, salt, choline and other essential food factors on experimentally produced hypertension will be discussed briefly.

Hypertension does not occur in the dog if the amount of dietary protein is increased unless there has also been interference with the renal circulation (240), and the results of some investigations have indicated that even after the application of Goldblatt-clamps, protein feeding does not further increase the blood pressure (111, 187, 196, 248). A high protein diet does however intensify the hypertension of rats which follows subtotal nephrectomy (26, 27) or the injection of nephrotoxic sera (230). Although diets low in protein prevent the development of nephrosclerosis and hypertension in rats treated with injections of LAP, similar changes induced by desoxycorticosterone are independent of the level of dietary protein (41, 199). A reduction of dietary protein and salt, or in caloric intake lowers the blood pressure of subtotally nephrectomised rats (118) and the hypertension can then be restored by the injection of adrenocorticotropic hormone (120).

The administration of 1.2 per cent sodium chloride in the drinking water of chicks produces nephrosclerosis (148, 216) and this may be accompanied by hypertension which persists as long as the administration of salt is maintained (149). Attempts to produce hypertension in dogs by increasing their intake of salt were unsuccessful (240) but more recently, Saperstein, Brandt and Drury (208) have reported levels of systolic pressure in rats of nearly 140 mm. Hg compared to a normal of 100, if two per cent saline was substituted for their drinking water for a period of one to four weeks. Salt hypertension persists after either nephrectomy or adrenalectomy, but is abolished when the salt water is replaced by tap water. It is of special

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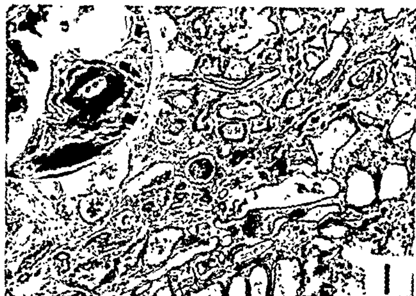
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interest that although adrenalectomy did not reduce the blood pressure, cardiac hypertrophy regressed (13). Restriction of dietary sodium is accompanied by a fall in the blood pressure of hypertensive rats following subtotal nephrectomy (103, 118), but this is not the case in dogs in which Goldblatt-clamps have been applied (100).

Attention has been directed to the relation of the lipotrope content of the diet (choline, methionine) to hypertension since a deficiency of these dietary factors results in extensive bilateral necrosis of the renal cortices in weanling rats ('hemorrhagic kidney' (94)) and adrenal cortical enlargement (178). A more slowly developing type of renal damage (unaccompanied by adrenal enlargement of any obvious degree) occurs in older animals and may eventually become widespread and severe after several months or a year (127) (fig. 1). After three to five months on a normal diet, hypertension develops in survivors of the acute type of renal damage (fig. 2) induced by a brief period of choline deficiency at the time the animals were weanlings (119, 129, 167). This hypertension is abolished if the animals are fed diets low in salt and protein, or if renal decapsulation is performed, and following either procedure the blood pressure is restored to high levels by the injection of adrenocorticotropic hormone (119, 122). Mature rats subjected to similar brief periods of choline deficiency (5 to 10 days) followed by normal diets did not become hypertensive in experiments performed by Moses (167) although Allerdyce, Salter and Rixen (2) reported opposite results. This latter group also found that the development of the hypertension in their animals could be hastened, but not intensified, by injection of small amounts of DCA. Hypertension is absent in rats maintained continuously for several months on a diet low in choline (232) and the hypertension present in subtotally nephrectomised rats is abolished by dietary choline deficiency (121). It is of especial interest that cardiac hypertrophy occurs in the absence of hypertension in mature, choline-deficient rats in which severe degrees of the chronic form of renal damage have been induced (128). It is not yet established if this has any relation to the reduction of cardiac hypertrophy despite the maintenance of hypertension following bilateral adrenalectomy in rats with salt hypertension (13). Further investigations of these and other problems related to the dietary production of hypertension will doubtless provide many interesting additions to our knowledge of the etiology of the condition.

Other dietary factors have been found which appear to have an effect on the blood pressure of experimental animals. Vitamin A and extracts from certain fish oils lower the blood pressure in hypertensive rats and dogs, and prolong the lengths of their lives (101, 105, 241). Clinical trials with vitamin A have produced conflicting results however. A deficiency of the heat stable fraction of the vitamin B complex was reported to produce





Figs. 1 and 2

normal

hypertension in rats (21, 22) but this has not been confirmed in other laboratories (166). A deficiency in vitamin E has been reported to lower the blood pressure of rats to subnormal levels (238) but other investigators have found that injections of vitamin E abolished the hypertension produced in rats by injections of DCA (2). The explanation for these apparently conflicting results awaits further investigations.

Renal Endocrine Function

Selye (217) has suggested that the epithelial cells in the walls of the renal tubules may act as a source of a renal hormone which affects blood pressure. By constricting the aorta of rats between the origin of the renal arteries and ligating the left ureter, he has produced what he terms, an 'endocrine kidney', in which the lumina of the tubules have disappeared and the epithelial cells multiplied, but other morphological characteristics of endocrine function, such as cytoplasmic granules, etc., do not appear to develop under these conditions. The evidence for a possible endocrine function' of renal tubules is as yet incomplete.

The presence of specialized cells in the media of the afferent glomerular arterioles has been recognized for a number of years. These were first described in mice in 1925 by Ruyter (206) who noted that they could be differentiated from the smooth muscle cells in the arterial wall by their epithelioid nature and by the frequent presence of granules within the cytoplasm. Other investigators have identified these cells in many other species including man (45, 81, 161, 162, 174), cat (81), rabbit (48), dogs (87), rat (81) and others. The cells differ in size and other respects in the various species, being most numerous in the cat and rabbit under normal conditions. Zimmermann (253) first described a specialized region in the portion of the distal tubule which lies between the afferent and efferent arterioles and which is characterized by an increase in the number of cells in the wall at this point. This he named the *macula densa*. Goormaghtigh (83) and McManus (161, 162) have pointed out that there is a constant and intimate relation between the juxtaglomerular cells and the *macula densa*. The name, juxtaglomerular complex, includes not only the specialized cells in the arteriolar wall at the glomerular pole, but also the *macula densa*. Both Goormaghtigh and McManus have suggested that there may be a functional relation between the *macula densa* and the granular arteriolar cells.

In every respect, the specialized arteriolar cells meet all the morphological criteria necessary to establish that they are capable of endocrine function. It is still largely a matter for speculation as to how such a function is involved in the regulation of blood pressure, if at all. It was first suggested that the cells might operate in a purely mechanical manner to

regulate glomerular flow by swelling or shrinking, and thus narrowing or widening the lumen of the afferent arteriole (29, 87, 206). Edwards (49) has objected to this hypothesis on the grounds that intermittency of glomerular flow in mammals and man has not been demonstrated. The consensus of current opinion appears to favor the view that the granules in the cells represent a precursor of some hormone which is liberated directly into the lumen of the arteriole, and that variations in the size of the cells are of little functional significance other than as indications of some phase in the production, storage or liberation of the hormone.

The possibility that the hormone may represent a form of renin or some substance with an ultimate pressor activity has been proposed by several investigators, most notably Goormaghtigh (83) and Dunihue (46) Some of the evidence in favour of such a concept may be briefly mentioned Hypertrophy of the cells has been reported in dogs made hypertensive by denervation of the aortic arch and carotid sinus (51). In the rabbit and dog following renal arterial compression, many afibrillar cells acquire endocrine cytological characteristics associated with hypertrophy and hyperplasia and with transformation of other muscle cells into afibrillar cells, which in the rabbit particularly, become granular (82, 85, 86). Dunihue and Candon (46) not only noted the increase in granular cells in the early stages of hypertension in rabbits with renal arterial constriction, but felt that there was a correlation between granule content, the amount of renin liberated by the kidney and the degree of hypertension. Other investigators (90) have reported that in dogs with one renal artery constricted, there may be no more than the normal distribution of granular cells in the contralateral kidney, whereas in the ischemic kidney they are easy to find and are increased in number. Hypertrophy of the cells in the form of small tumor-like masses have been reported in the early stages of pre-eclampsia [illegible]

and in malignant hypertension, but not in the benign phase. Others however have found that enlargement of the cells in Goldblatt-dogs or in other forms of experimental hypertension, is inconsistent (10), or have failed to observe any constant alteration from the usual appearance (38, 209, 219, 225). The demonstration by Grollman that a sustained hypertension can exist in the absence of both kidneys (and therefore in the absence of juxtaglomerular cells or their secretion) is the strongest argument against the views of Goormaghtigh and his supporters.

The opposite concept that the juxtaglomerular complex may secrete a substance which depresses the level of arterial pressure or counteracts a pressor hormone has not been actively supported by many investigators,

although both Dunihue (46) and Goormaghtigh (84) have considered this possibility. The evidence cited above does not contradict this view for if there is an increase in the granule-content of the juxtaglomerular cells of a kidney during the first few weeks after the application of a Goldblatt clamp, this may represent an active phase in the secretion of a depressor substance which is attempting unsuccessfully to return the blood pressure to normal limits. The fact that the granules are difficult to demonstrate after the height of the elevation of blood pressure has been attained might indicate an exhaustion of the depressor-secreting mechanism, and this very fact could be responsible for the maintenance of the hypertensive state. As indicated in the section concerning the adrenal cortex, there is considerable evidence that secretion of the desoxycorticosterone type of hormone may represent the source of the pressor substance, which if either increased or unopposed by a supposed hormone formed by the juxtaglomerular cells, would result in hypertension. Dunihue (47) showed that injection of DCA prevented accumulation of granules in the specialized cells following adrenalectomy, and we have found a very striking change in the granule-content of normal rats injected with DCA, especially if frozen sections are employed (125) (figs. 3, 4, 5). It has also been demonstrated that what might be interpreted as a storage phase, develops in these cells in the kidneys of rats fed a diet low in vitamin E for several weeks (126). In these experiments an inverse relation could be demonstrated within the group of E-deficient animals between cardiac size and numbers of granular cells. A useful working hypothesis would therefore be that liberation of a secretion of the juxtaglomerular complex may be stimulated by circulating hormones of the desoxycorticosterone type. The rate of liberation of the hypothetical juxtaglomerular hormone might thus be regulated so that it would conteract the pressor effect of desoxycorticosterone.

Conclusions

The light cast on the problems associated with experimental hypertension by the findings of Braun-Menendez, Grollman, Handler and Bernheim and others, will doubtless lead to the rapid formation of many important new concepts of this disease. If Grollman and his associates are successful in isolating a depressor substance from normal kidneys, this will have obvious clinical importance (109, 110, 124, 245). The well known contributions of Goldblatt considered in conjunction with the knowledge provided by Selye and others in regard to the adrenal cortex, appear to be opening a pathway which may lead to a logical explanation for the etiology of essential hypertension in man. The fact that acute lesions of the kidneys and adrenals in young animals may be followed by hypertension in later life,



Figs 3, 4, and 5

... Granules (black) can be seen in the specialized juxtaglomerular cells ... arteriole in the kidney of a male, 20-gram, mouse ... granules found in a normal control ... ies was much lower. Frozen section;

... al sections, respectively, of renal ar- ... cimately 45 minutes after receiving a ... Note the large

... lation, ...
plate were prepared by the ... Merritt ...

despite apparent recovery from the initial injuries, suggests that clinical gerontologists might profitably seek for episodes in the early years of life which may have laid the basis for the development of hypertension in the adult patient. It may even prove that this same principle applies to some of the other major problems of ageing, such as cancer and diabetes.

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15

THE THYROID, PANCREATIC ISLETS, PARATHYROIDS, ADRENALS, THYMUS AND PITUITARY

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As differentiation and specificity in the endocrine glands appear as marked in long life as in short life species, and since the "accidents of living," such as infections, dietary deficiencies or excesses and other forms of stress on the individual are on the whole probably not greater in the short life species, the primary "timer" of the life span is evidently hereditary factors not essentially conditioned on tissue differentiation. Accordingly, the hypothesis that the elements of senescence are inherent in the processes of differentiation does not seem fundamental. On this hypothesis the problem of ageing embraces the entire life span of the individual. Even if this hypothesis did express some truth, it is not very useful at the present stage of biology, in part because of the lack of adequate methods for testing it. We shall therefore focus our attention mainly on the late adult and the advanced age periods, since here we have both data and methods of testing their interpretation, albeit much of the data may be irrelevant or inconclusive, some of the methods need refinement, and most of the experimental material requires improved control.

The Need for Controlled Data

Well controlled data on age changes in the functions of the endocrines, apart from the gonads, is at present very meager. Most of the data relate to gross weight, and histological structure of these glands relative to age. These structural findings cannot at present be given definite functional interpretations, partly because of the very large "factors of safety" in all of these glands. Great decrease in gross size, or great reduction in size or number of cells, may not therefore signify reduced output of hormones.

Even the quantity of hormones per weight of glands, at different ages, cannot at present be related to hyper- or hypo-activity, even were the methods of extraction reliably quantitative, because we do not know the precise relation between production, storage and secretion. Before a significant chapter on ageing of the endocrines can be written, we must have data on the actual output of the hormones by age in controlled material. Observations on the concentration of the hormones in the blood, and in rare cases in the urine, in controlled material are urgently needed. We stress "controlled material" for the following reasons:

1. The structure, and probably the activity, of at least some of the endocrines is related to the diet, both as to quality and quantity. Controlled material would thus seem to call for an optimum diet throughout the period of observation. This is particularly the case with the vitamins, and with iodine, in the case of the thyroid glands. The frequent, if not invariable impairment of the digestive processes with advanced age (see Ivy, Chapter 22) may, indeed, be a factor in slowing up hormone production through the dietary factor.

2. Some of the endocrines appear to be subject to histological, if not functional, injuries by systemic or focal infections. When these cannot be avoided in controlled material, their number and relative severity should at least be part of the record when the data on change in endocrine function are to be related to age, directly or indirectly.

3. The factor of heredity might be ignored when observations are made on the hormone concentrations in the blood of the same individual, from youth to old age, or when the structural changes in the glands are followed in the same individual by the biopsy method. But heredity becomes important when random observations are on a mixed population, the observations, at that, being made on different individuals, for the different age groups. The fact that some individuals develop diabetes at the age of 10, others at the age of 50, while others may live to 90 or 100 years without diabetes, may or may not be related to an hereditary resistance or endurance factor in the pancreas complex. Similarly, some do develop what appears to be spontaneous myxedema before 40, while others do not show it clearly even at 80. But we cannot assume at present that such hereditary "endurance factors" are not involved, even though they do not tell the whole story.

4. Since there is fairly good evidence that structural as well as functional changes in the endocrines are induced by impaired blood flow through these glands, "controlled material" implies not only parallel observations on the cardiovascular system, especially in individuals of advanced years, but renders observations on the endocrines on those individuals who reach very advanced age with the minimum of vascular impairment particularly

important as the latter would serve as a check on the endocrine age involution, if any, in the presence of inadequate blood flow.

5. In addition to diet, infections, heredity and vascular adequacy, the attack on the role of the endocrine in the ageing process is further complicated by the growing evidence of some dependence, in the matter of structure and hormone output, of each endocrine on the hormone output of one or more of the other endocrine glands. In this respect the gonads seem to form a significant exception. While the very life of the gonads depends on hormones from the pituitary, the thyroids, and possibly the adrenal cortex, total loss of the gonad hormones, as by castration in early adult life, has so slight influence on the other endocrines in direction of impaired function that no definite syndrome of hypofunction develops, there appears to be no premature ageing, physically or mentally, reliably established and there seems to be no shortening of the life span. But as to the complex interdependence of the other major endocrines (thyroid, anterior pituitary, adrenal cortex, the pancreatic islets), there is now no doubt. And so our "controlled material" on the role of the endocrines in the ageing process involves simultaneous checking of the functions of at least five of the major endocrines at each age level.

The earlier theory that the gradual failure of the endocrines is the main factor in the ageing process (26, 36, 21, etc.) has not been substantiated by subsequent work, although it must be granted that this work is largely fragmentary and inconclusive. The clear case of the gonadal atrophy with age, particularly the ovaries in the human species (see Chapter 26), has rendered this general theory plausible and attractive. But on closer analysis, the atrophy of no single endocrine or group of endocrines can by itself readily account for the ageing process. For example, Addison's disease (impaired Adrenal Cortex) is rare in people past 50 years of age; only about a third of the cases of myxedema occur in people past 50; while active acromegaly (hyperfunction of the anterior pituitary) and toxic goiter (hyperthyroidism), particularly the latter, are not infrequent in people of 50 to 80 years of age (7, 61). In more recent years the glamour of the gonads has tended to ascribe ageing mainly to failure of these glands and has given rise to the spectacular pseudo-science of "rejuvenation" via the route of the gonad hormones or gonad implantation.

If the data so far adduced are even approximately reliable and our reasoning so far sound, it should be apparent to the reader why past observations in the ageing of the endocrines, even by competent and industrious investigators, have so little scientific value for our present task. The past interest in the ageing process has centered largely on man, where we cannot, or specifically have not to date, controlled the factors of diet, heredity, infections, and vascular adequacy. And our information on the

interdependence of the major endocrines is not only very recent, but is *even now replete with gaps and guesses*. The ageing processes in the endocrines alone make a full time or major biological problem, calling for large material resources and the long pull. Without both, the scientific perspicacity naturally turns to the things that can be done, with present facilities, even if these may seem less interesting and fundamental.

Obviously the central theme or problem is the hereditary "time clock" in the endocrine glands themselves. And this includes the endocrine interrelation factors. This is the direct endocrine timer of the adequate life span. But it is equally evident that diet, infections, and vascular inadequacy may so impair endocrine function as to render the hormone output inadequate for the optimum bodily needs. Thus, by indirection, the endocrine may also here act as one of the timers of the adequate life span. In fact, some of these relations seem to operate in the manner of the vicious circle. Thus, hypothyroidism and diabetes reduce the resistance to infection and repeated or prolonged infections appear to cause further weakening of the "factors of persistence." Hypoparathyroidism tends to unstabilize the nervous system, and this, in turn is probably not a good omen for digestion, metabolism and the cardiovascular system. While we propose to analyze our present data from both points of view (the direct and the indirect endocrine timer of the adequate life span), the reader is urged to temper and if possible improve our conclusions by the contributions of the other authors of this book.

The Thyroid

No organ or tissue in the human or animal body seems to work up to par in the total absence of the thyroid hormone. This has been made out most clearly in the experimental animal, notably the rabbit, in which species accessory or aberrant thyroid tissue is rare, so that total thyroidectomy can be accomplished. Total absence of the thyroid hormone in man appears to be very exceptional, but varying degrees of hypothyroidism in man have been studied extensively, and in all essentials these data on man conform to the findings in the better controlled experimental animal. All organs do not seem to be impaired to an equal degree after total thyroidectomy. For example, *the life of the gonads are more profoundly impaired* than is the function of the pancreatic islets. The central defect induced by total absence of the thyroid hormone appears to be the reduction in the rate of tissue oxidation. Impairment of growth and repair, decreased resistance to infections, tendency to fatty degeneration in muscle and many other tissues may be sequelae of *the impaired oxidation. The* following, fairly well established data are on the whole consistent with the theory, but are by themselves no proof that the production of the thyroid

hormone, after attaining its normal maximum at puberty, decreases with advancing age by the gradual running down of the hereditary time clock.

1. The slow, but gradual reduction in the basal metabolic rate in otherwise healthy men, after the age of 20 to 25, seems well established. There is no reason for thinking that other animals do not exhibit the same phenomenon, though actual data are not yet at hand. Is the lowering of the B.M.R. with age due directly to a parallel advancing hypothyroidism? If so, there should be other evidence of increasing myxedema with age besides the low B.M.R. Those who (like Lorand) argue that this is the case appear to us to give undue weight to superficial resemblances, such as occasional increased body weight, dryness of skin, and failure of hair growth on the scalp. In the total body oxidation as measured by the B.M.R. method, the skeletal muscles seem to contribute the major factor. Now, decreased skeletal muscle efficiency, muscle tone, etc., not to speak of fatty degeneration and other indices of muscle atrophy with advancing age, whatever be the cause or causes, appear to be on a firmer scientific basis than is age involution of thyroid function. The primary thyroid responsibility for the age changes in the skeletal muscles is not established and appears to us improbable, because were those the only causal relations, we ought to see a parallel impairment of brain function, as is the case in true cretinism and myxedema. On the contrary, intellectual processes may in man actually show an ascending curve, while physical capacity and endurance (mainly muscle efficiency) are descending.

2. There is a superficial resemblance between the impairments appearing in the skin and the hair with advancing age and those induced by varying degrees of hypothyroidism. But it is well known that loss of the hair color or even baldness of the scalp may occur in some people as early as the age of 25 to 30, with no other indices of hypothyroidism. It is further known that at the very time that the age involution of the human scalp hair is advancing, hair on other parts of the body (eyebrows, nares, ears, etc.) may exhibit increased growth. Moreover, the skin and hair defects due to true hypothyroidism can be largely checked by administration of the thyroid hormone. If the thyroid hormone has the same efficacy in the case of loss of scalp hair or hair color with advancing age, the numerous and assiduous inventors of "hair restorers" have certainly overlooked a bet!

3. In the experimental animal at least marked hypothyroidism somehow produces a lowered resistance to infections, particularly infections of the respiratory tract, such as sinusitis, bronchitis and pneumonia. In man the incidence of infectious diseases in childhood, adult life and advanced age is complicated by the immunities induced by several types of infections usually occurring in childhood. In infections where little or no immunity is induced, such as colds, pneumonia and many of the strep-

tococcal infections, the greater incidence of these with advancing old age is not yet clearly established. What appears to be indicated is a reduced capacity to combat these forms of infection in the old, and hence the greater prevalence of chronic arthritis or rheumatism, the higher mortality from pneumonia, etc., in the aged. This is consistent with the theory of primary hypothyroidism with advancing age, but since these facts can be otherwise interpreted, they constitute no proof of the theory.

4. In the experimental animal total absence of the thyroid hormone, or at least a very marked hypothyroidism induces weakness and atony of the skeletal muscles, accompanied by fatty degeneration in these muscles (as well as in the heart muscle). We are not acquainted with any data on biopsies on the skeletal muscles of human cretins and myxedematous adults, hence we cannot at present view the skeletal muscle weakness and atrophy and signs of degeneration, or the myocardial degeneration in advanced age, as causally related to a primary hypothyroidism. It seems to us the same caution is called for in relating other age involution or tissue atrophies, such as arterial sclerosis, to thyroid function. A certain degree of chronic hyperthyroidism seems to induce myocardial degeneration and sclerosis, and is thought by some to be one factor in inducing or accelerating arterial sclerosis. The fact is that the primary relation of the thyroid hormone, hypo or hyper, to these usual tissue changes with advanced age is as yet an open question.

5. The literature contains considerable information on the usual gross and microscopic changes in the human thyroid gland from early intra-uterine life to ripe old age. If we eliminate the instances of frank and possibly primary thyroid disease (hypo- and hyperthyroidism, thyroid tumors) the gland appears to attain its maximum normal size (and possibly function) at the age period of 15 to 20. At this age there appears to be considerable replacement of the epithelial cells, as indicated by the numerous cell divisions. The acini tend to be fairly round in outline, uniform in size, and lined with a single layer of cuboidal epithelium. According to Cooper (8), based on human postmortem material, the thyroid of people from 60 to 80 years of age is reduced in size, the follicles and the cells are smaller, the vascular supply is reduced, there is much less mitosis seen in the epithelial cells, the colloid may be absent from many of the vesicles and the colloid, when present, appears less dense. There is definite increase in the connective tissue (sclerosis). Less notable changes in the thyroid are described for the adult period of 40 to 50. McCarrison states that the human thyroid after the age of 40 shows less colloid, sclerosed blood vessels and increased connective tissue. Dogliotti and Nizzi-Nuti (11) report on the structure of the thyroid of 50 late adult and aged people, eliminating those of frank thyroid disease, and the thyroids of patients

dying with severe infections. According to these authors, in the thyroid of the "pre senile" (50 to 65 years) the follicles are reduced in size and in colloid content, while during the "senile period" (over 65) the follicles are so reduced in size that the cavities are practically obliterated, with no colloid present, but there is some increase in the connective tissue. These authors interpret these age changes in the thyroid gland as indicating an increase in the output of the thyroid hormone with advancing age, the very opposite of the views of most authors on the thyroid-age problem. Smith (59) describes atrophic changes in the thyroid gland of old mice, similar to those noted in old people.

There are some data indicating a reduced amount of iodine per weight of gland in aged human thyroids. This work requires repeating with our present superior chemical methods, and on controlled material, before it is worth while to even essay an interpretation. From the field of frank hyper- and hypothyroidism in man it appears that reduced iodine content per weight of gland may be present with lessened as well as with increased output of thyroid hormone. And the minimum iodine content of the gland commensurate with adequate thyroid hormone turnover for the age of the individual is not yet known.

Most anatomists, pathologists and, indeed, internists and physiologists are probably inclined to interpret the above gross and microscopic changes in the thyroid gland of late adult life and advanced old age in man as evidence of primary hypothyroidism. But we are impatient with mere interpretation where we may experiment and thus know. In view of the very large factors of safety in the normal thyroids, only controlled experiments can tell how far reduction in gross size of the gland, reduction in size and number of the epithelial cells, reduction in iodine and in colloid, reduction in vascularity and increase in connective tissue can go before the output of the thyroid hormone falls below what may be determined as the normal or optimum rate.

6. Experimental as well as clinical evidence indicate that the thyroid hormone is one of the many factors concerned in the water balance in the tissues. At any rate in marked hypothyroidism there is a tendency to increase tissue water, while the initial reduction in body weight by hyperthyroidism is in part a matter of loss of tissue water through diuresis and sweating, followed by increased thirst, water ingestion, and a tendency to a continuous higher level of urine output. Now that tissue desiccation, rather than tissue hydration appears to be the rule in the ageing, the matter is referred to here as one which by itself is not consistent with the view of significant hypofunction in the thyroid of advanced age.

7. While the possible role of the gonad hormones (especially the female) and the anterior pituitary so-called thyrotropic substance in the

regulation of the normal rate of thyroid hormone secretion is by no means clearly established at least for the dog, yet we have these facts: in some species, at least, a temporary thyroid hyperplasia and increased hormone output by something present in an extract of the anterior pituitary; the normally maximum thyroid size and possibly function in the adolescent years; the apparently more frequent occurrence of hyperthyroidism during the years of most active gonad function; the more frequent occurrence of hyperthyroidism in the human female than in the human male. The gonads atrophy with age. The ageing anterior pituitary exhibits some changes that may indicate but do not prove reduced hormone output. We advance no theory and offer no interpretation, as we do not know the facts We merely refer to these indices as something to be considered in any well planned research project on thyroid and age.

8. Marine and Baumann (37), and Scott (57), report that in rabbits and cats adreno-cortical insufficiency raises the B.M.R. when the thyroid gland is intact, but not after thyroidectomy. This is being interpreted as an inhibitory action of the cortical hormone on the secretion of or on the systemic action of the thyroid hormone. The fact itself calls for reinvestigation The interpretation will probably not stand, for increased B.M.R. is not an element of Addison's disease in man, and Schachter has been unable to lower the B.M.R. in normal dogs or in dogs rendered hyperthyroid by injecting large quantities of an active cortical extract (personal communication).

9. Some thyroid growth disturbances and possibly disturbance of function may be prevented by iodine therapy and can therefore not be primarily hereditary. And yet both cretinism and myxedema do appear in populations where iodine ingestion seems to be at least minimal and where iodine therapy is of little or no remedial value. In these cases defective hereditary thyroid potentials must at least be considered. Myxedema in many may come on in late adult life without previous history of earlier thyroid failure, even though frank myxedema appears not to increase with the advancing years beyond 40 to 50. It is, of course, entirely possible that these premature thyroid failures are not hereditary, but due to other types of injuries. If real thyroid heredity enters here, it is probably exceptional only in degree. That is to say, heredity may time the life span of all thyroid glands, but for the present, and excluding frank thyroid disease, the thyroid life span appears not to be the limiting link in the life, or rather the adequate life, of the aged. We say this despite the advocates of the use of thyroid substance as a helpful therapy for the years of decline, and even the reports of "curing senility" (!) by thyroid administration. When thyroid substance is found to have real value in the aged, its action is probably non-specific. The very aged may feel somewhat better tempo-

rarily after any stimulating therapy, such as a warm bath, massage, strychnine, ephedrine, caffeine or even whiskey

10. Many dietary factors, besides the quantity of iodine, appear to modify thyroid structure, if not function (40, 28, 29, 38). These factors may play a role in the thyroid structure and function of the aged man and animal, where qualitative and quantitative food intake is in many cases likely to be less than the optimum This will probably be a disturbing factor in the study of thyroid function in the very old individual, even in controlled populations, as appetite, hunger, digestive power and metabolic efficiency may present barriers to conclusive experiments

The Pancreatic Islets

1. Much water has gone over the dam on the pancreas-diabetes problem since the classical observations of von Mering and Minkowski on pancreatectomized dogs. The theory of pancreas hormone action has mainly proved out, over the theory of a pancreas detoxication function, thanks largely to that other classical work of Banting, Best, Collip, and McLeod. But with growth of understanding has come increasing complexity: the islets and insulin are not the only factors. There is in all probability a second pancreatic hormone, the lipocaic of Dragstedt, involved in the carbohydrate-fat interchange, at least in the liver. The work of Houssay and Biasotti (27) showed a probable anterior pituitary factor, while the work of Soskin and others (60) points to important relations of the liver and, in all probability, the blood capillary and muscle cell permeability. The possibility that the second pancreatic hormone (lipocaic) is identical with the omnipresent cholin seems to be dispelled by Dragstedt's latest work, in which he has succeeded in so nearly completely removing the cholin from his extract that the trace of cholin left is too small to have any influence on the fatty livers of pancreatectomized dogs controlled in insulin (personal communication). But in experimental and in spontaneous human diabetes the pancreatic islets and insulin still constitute the one indispensable link in the diabetic processes. All human diabetes appear to be influenced, in the direction of control, by insulin; and in the otherwise normal animal impairment or destruction of the pancreas seems to be the only sure way of reproducing true clinical diabetes. But we see no satisfactory explanation of the fact that the human diabetic patient needing even large quantities of insulin seems to get along without the lipocaic being supplied and without developing a degree of fatty degeneration of the liver leading to death, while the pancreatectomized dog on adequate insulin control and without lipocaic dies within a few months with extremely fatty liver as a probable factor in the death. Of course, human diabetes is rarely absolute, some islet function usually remains. And there

are indications that in the usually more severe form of juvenile diabetes fatty livers may develop, even under good insulin management. The lipocaic probably comes from the islets, as shown by the fact that on the nearly complete degeneration of the pancreatic tissue producing the external secretion following ligation of the ducts, the islets remain relatively intact and neither diabetes nor fatty liver develop. If, as seems probable, the insulin and the lipocaic are produced by different islet cells, there may be a differential impairment of these two types of cells in human diabetes. Should this prove true, we may have to consider the pancreas factor (lipocaic) in other forms of fatty degeneration of the liver, not related to diabetes as we now think of this disease.

2. Before any generalizations are made anent the role of the pancreas islets in the ageing process, the following questions must be cleared up:

(a) While true spontaneous diabetes is not unknown in domestic animals, notably the dog, this disease appears to be distinctly more common in the human species. This may be a matter of lack of information in the case of the domestic animals. On the other hand, it may be due to a greater hereditary potential of the islet tissue in animals below man. There are some indications that the islets may be injured, temporarily or permanently, by such factors as infections, extreme dietary disgression, marked hyperthyroidism, etc. But man is not the only species prone to overeating and subject to all manner of infections, temporary and chronic.

(b) Again, in animals like the dog and the rabbit, there is normally so much excess islets present that from 9/10 to 15/16 of the islets may be removed before the sugar tolerance is so reduced that the Sandmeyer type of diabetes shows up. If a somewhat greater portion of the pancreas is left in the animal this remnant hypertrophies, in some cases to near the size of the original pancreas. We have no such accurate data on the factors of safety in the islets in the non-diabetic man, to be sure, but there is scarcely any exception to the rule that once a person, young or old, becomes a diabetic, he is a diabetic for life. The degree of diabetes may become more severe with time. Even under controlled conditions the diabetes rarely becomes less severe. That means, practically, the absence of regenerative capacity of the islet tissue (including the cells of the pancreatic ducts) in the human diabetic. Is this also true for the non-diabetic man? We are reluctant to accept, without better evidence, such a profound difference between man and the lower animals. There is, of course, a marked difference between surgical removal of part of the pancreas in the healthy animal and the impairment of the pancreatic islets by infections or overeating in man. The first procedure leaves the pancreas remnant normal, although possibly subject to overstrain; the latter may hit mature islet function and regenerative power with equal severity and

permanency. To the extent that such injuries are favored by hereditary weakness in persistence, that weakness may be primarily in the capacity of regeneration.

(c) Statistics show unmistakably that obesity predisposes to diabetes in man (31). But which is the horse in this combination? The fact that overeating renders existing mild diabetes more severe, that partial starvation of a diabetic individual renders severe diabetes milder, that mass starvation reduces the incidence of new cases of diabetes in a population would seem to make the diet (overeating) the primary factor. Now, overeating to the point of marked adiposity is not unknown among animals (hogs, steers, some animals preparing for hibernation) without diabetes, or more specifically, without information that diabetes is the sequel. In the case of the domestic steer and hog, the answer may be that the time is too brief. The hibernating animal may give the islets a chance to recuperate in the subsequent months of starvation. But there are the permanently very obese marine mammals. Work could be done on the seal. The hog, as measured by alimentary glycosuria, indicates low sugar tolerance, but that does not necessarily mean reduced islet capacity and predisposition to diabetes. If it should turn out that the "prediabetic" glucose tolerance curve (30) really means eventual diabetes (barring death by accident), the glucose tolerance test might be a useful tool in securing data on the islet adequacy in animal populations.

The precise relation of direct and indirect nervous states to the islet-metabolism machinery is still an unknown. We have reports that "mental strain" may aggravate an existing diabetes and call for larger doses of insulin, but even if so, such influences are probably both superficial (glycogenolysis) and temporary. We may assume that much of the acute but temporary fear of wild animals and primitive men has shifted to the prolonged anxieties of civilization. On a vascular basis the latter may do something to the pancreas islets, but hardly more so than to the [illegible] and the gut.

there is a very definite decline (32, 15). Since the onset of the defect may be gradual and in its incipient stages may go unrecognized, the true onset of incidence (i.e., the beginning) falls probably further to the left (lower age periods) than present statistics indicate. The appearance of true diabetes in infants at the age of 1 or 2 years and the absence of diabetes in men and women at the age of 80 would seem to indicate that hereditary persistence factors in the islet mechanisms are involved, irrespective"

how much infections, dietary digression and other possible types of strain may be contributory. The latter may help to explain the increasing incidence of islet breakdown up to the age of 50, but neither heredity nor environment (internal and external) can account for the reduced incidence of diabetes in people past 60. It can scarcely be gonadal atrophy, since castration appears to have no such profound influence on the carbohydrate and fat metabolism. If, speaking in percentage of the age population, more people past 60 eat more sparingly, in relation to their physiological needs, than is the case in the population below 60, we do not yet know it. We can conceive an hereditary persistence factor in the islets that would still be adequate even at the (alleged) age of Tom Parr. But even this assumption does not readily square with the reduced incidence of diabetes in old age. A "quantum theory" of inherited persistence might help, but such a concept does not fit the curve below 60. Perhaps the present statistics are unreliable.

4. Atrophies, hydropic degeneration, sclerosis, etc., have been described in the pancreas (islets as well as the other tissue) of adult and old people, diabetic and non-diabetic (43, 2). The earlier workers found more degenerative changes in the islets of the diabetics than in the non-diabetics of similar age groups. According to Fisher and Scott (17) the fetal pancreas is six times richer in stored or preformed insulin than is the pancreas of adult cattle, but the decrease in stored insulin advances very slowly after the seventh month of age. In man the pancreas as a whole seems to be labile or readily damaged by dietary digression as well as by local and systemic infections. When the islet factor has been greatly reduced by surgery, high food intake seems to induce or aggravate atrophic or degenerative changes in the islet cells (2). In regard to infections, it is assumed that these damage the prediabetic islets permanently, but the only thing we really know in the matter is this: infections, as well as many other things, increase temporarily but rarely permanently the insulin requirement of the diabetic man. This may or may not be solely a matter of depression of an already defective islet mechanism. It probably is not. At any rate it seems unlikely that infections by themselves should induce permanent islet damage in the prediabetic but not in the diabetic state. If it is infection, it must be infection plus. The earlier accounts of rather marked histopathology in the pancreas islets of human diabetics have been somewhat challenged by later observers, and it is fair to say that in some cases the islets, even of a patient dead in diabetic coma, may show less pathology than one would expect, on the basis of the large factors of safety in the islet mechanism of dogs and rabbits. But this is probably very superficial reasoning. For we do not know when and to what degree the anterior pituitary or the thyroid may render a moderate diabetes more

severe, and we must know more about the state of the liver and the degree of reduction in insulin output before the islet cells show any histopathology. *Even more to the point, we should know the amount of insulin in the blood* of these people who are reported to die of diabetes, with so little evident pathology in the islet cells. Not that we would urge less work, or especially less quantitative work, on human diabetics and so-called prediabetics of all ages, but owing to the unsatisfactory control of human material even at best, a prime consideration now is a concerted attack on a controlled animal population through its entire life span, with the technique on tissues, body *fluids, and hormone quantitation now* available. *Then, and not till* then, will we be in a position to say, for one species at least, whether or no the islet mechanism alters with age to such an extent that it becomes one of causative factors in the general ageing process. For the present the only thing we can say with certainty is that the depression of the islets mechanisms (causes unknown, but probably in part hereditary and dietary) leading to diabetes handicaps age and tends to shorten the life span of some people. For the optimum control of the diabetic state through diet insulin, and possibly lipocaic, is not readily maintained throughout every day for months and years. Tolerance in the diabetic does fluctuate from causes so far unknown, and less than optimum control seem to reduce the resistance to infections.

Arterial sclerosis is a fairly constant phenomenon in ageing men and in such other animals as have been adequately investigated to date (see Chapter 13). It may be noted in connection with islet function and diabetes that earlier or more extensive arterial sclerosis appears in many diabetic individuals of early adult age even when the diabetic condition seems adequately controlled by insulin and diet. The precise islet factor in this phenomenon is obscure. Since reduced islet function appears to predispose to infections, and infections stand at least accused in the etiology of arterial sclerosis, one of the causes may be disclosed up that alley.

The Parathyroids

1. According to Cooper (8) the human parathyroids do not attain adult size and histological structure until the period of puberty and adolescence. Gilmour and Martin (19) report that the parathyroids of the human male attain their maximum size at 20 to 30 years of age, when a gradual *decrease in size sets in, while in the human female these glands* increase in size till the age of 50. The importance of these developmental changes, *as well as the reported appearance* of relatively large cells with eosinophile granules in the parathyroids of young adults, is difficult to evaluate at present. The effects of parathyroidectomy do not seem to differ in youth from those in later years, except that they tend to set in earlier and be

more rapidly fatal in very young animals. Only one hormone, the chemical involved in calcium and phosphorus balance in the body, is even approximately known to be derived from these glands. The increase in connective tissue in the gland in early adult age and its fairly regular distribution around the epithelial cell groups tend to give the gland the appearance of embryonic thyroids. Colloid has been described both in and in between the gland cells, but whether this is a sign of secretion or of degeneration is not yet known. The difficulties in interpreting histological findings in the light of function in these glands are illustrated by the fact that Houssay and others (27) report impairment of the parathyroid after total hypophysectomy. Now it appears well established that no symptom of functional deficiency clearly related to the parathyroids follows ablation of the pituitary gland.

The potency of the theory of detoxication as a parathyroid function has been weakened by the discovery of the hormone mechanism. The greater susceptibility to systemic disturbances from gastro-intestinal disorder in the parathyroidectomized animal may be secondary to the upset in the blood-tissue calcium balance. According to Cooper (8) the blood supply to the human parathyroids increases with age. This calls for verification.

Like most of the other endocrines the "factors" of safety in the parathyroids are very large, at least four to five times the minimum needs, and the parathyroids appear to have about the same growth and regenerative capacity as the thyroid tissue.

But several additional baffling facts remain to plague the workers in the parathyroid field: (*a*) the periodicity in the severity of some of the hypoparathyroid symptoms; (*b*) the gradual adjustment of the experimental animal (dog) to apparently total absence of parathyroid hormone and low (4 to 6 mg. per 100 cc.) blood calcium, provided life is saved in the first 5 to 6 weeks after the total parathyroidectomy; (*c*) the lack of indication of a similar adjustment in man; (*d*) the temporary efficacy, but frequent failure after months, particularly in man, of calcium or parathyroid hormone therapy, especially the latter, in frank hypoparathyroidism.

2. *The parathyroid hormone, together with vitamin D, appears to be* involved in the absorption and elimination, as well as with the actual deposition or stability of the tissue calcium. The actual level of the calcium in the blood is in part a function of the concentration of the plasma proteins, the greater part of the blood calcium existing there as a calcium proteinate. Hypoparathyroidism lowers the blood calcium and increases its excretion, largely at the expense of the calcium in the bones. In hyperparathyroidism (which may occur spontaneously in man in cases of hyper-

plasia of the glands) the blood calcium is elevated, also largely at the expense of the bone calcium. So we have, as is to be expected, the opposite influence of the hypo and hyper states on blood calcium concentration, but the same effect (but not in degree), that is, depletion of the bone calcium. The level of dietary calcium seems not to play a major role in these complex parathyroid hormone relations, but it is, of course, important as a long run factor. Significant hypoparathyroidism seems always to lower the plasma calcium below the normal, and thanks to the good quantitative methods for estimating the calcium content of the blood now available, and the ease of securing, from man and animals, the quantity of blood needed for such determinations, we seem to have, provisionally at least, a good measure of parathyroid hypo-function in any species at any age. The situation is less satisfactory, as regards parathyroid hyperfunction, because information so far indicates that much calcium may be taken out of the bones, under excess parathyroid hormone influence, without raising the plasma calcium much above the high normal. We need not point out that present methods of parathyroid hormone isolation are too crude to yield anything of quantitative value either as to the blood or the parathyroids in youth and old age.

3. There are, at present, no clear indications either in the parathyroids themselves, or in the general course of the ageing processes, that hypo- or hyperfunction of the parathyroids play any significant role in the impairments of the aged. Of course, we have no data on controlled material. But the blood calcium in man appears to remain within the normal limits up to 80 years and beyond. The calcium content of the bones of the aged may be "normal," increased or decreased, but there is no clear evidence that the failure or the excess of parathyroid hormone is involved in any deviations from the supposed "normal." There appears to be a definite decrease in the power of healing or repair of bones in old age, and the parathyroid hormone does seem to influence both osteoblasts and osteoclasts, but changes in the hereditary potentials of these cells must first be discounted before we can consider parathyroid hormone factors, as the land lies now. Various forms of nervous instabilities, such as paralysis agitans, are not infrequent sequelae of the ageing of man, and deficiency of parathyroid hormone produces instability in the nervous system. But hyper-excitable nervous states appear at any age, and despite much work to date clear involvement of the parathyroids seems limited to the tetany of hypoparathyroidism.

In the chronic hypoparathyroid animal (dog), certain dietary digressions, physiological and environmental strains seem to call for more parathyroid hormone, or at least, to bring the state of hypoparathyroidism into clearer view. But on the whole, these are strains of youth and younger

adult life rather than those of old age. There are other indications (in the case of the rat) that diet and environment (temperature) both influence the severity of some symptoms of hypoparathyroidism.

Because of the importance of the parathyroids in the calcium metabolism, the query: What role (hyper or hypo) does parathyroid hormone play in the increased deposition of calcium in so many tissues, notably the blood vessels and the lens, with age, is to the point and must be included in any real solution of the ageing problem.

The Adrenals

Armchair biologists have found little difficulty in pointing out the almost perfect parallel between the symptomatology of ageing (in absence of specific disease) and that of impaired adreno-cortical function, such as general asthenia, impairment of digestion, tendency to increased pigmentation of the skin, low basal metabolic rate, etc., and thus make out a plausible case for adreno-cortical failure as an important causative factor in the decline of the organism as a whole in what we consider advanced age for the species.

The usual hypertension in advanced age does not fit this picture, for one of the cardinal symptoms of significant impairment of hormone production by the cortex is profound and lasting hypotension. Turning to the adrenal medulla, and ignoring for the moment the above theory, excess adrenalin output was for a time seriously thought to be one of the significant factors in inducing or accelerating the usual arterial sclerosis found in the aged. Hence, the cortex contributes to the ageing process via hypofunction. Turning another intellectual somersault, we could drag the emergency theory of medullary function into the ageing nexus, for surely the aged individuals or at least those of very advanced age are progressively less able to meet all manner of physiological emergencies. They can't stand up in a fight even to a junior Dempsey or Louis, and in a marathon they will lose to a Nurmi, even when allowed a twelve mile handicap Thus, the medulla could contribute to the general ageing process, but this time via hypofunction. What are the *facts?*

The medulla and adrenalin

For some years the theory of an adrenalin factor in arterial sclerosis has seemed exceedingly anemic from lack of factual sustenance. Stopping nearly all secretion of adrenalin in patients and experimental animals by adrenal denervation or by bilateral section of the major and minor splanchnic nerves does not induce hypotension nor does it seem to significantly or lastingly reduce hypertension. There is no reliable evidence of a change in the rate of adrenalin output with age either in man or animals. The sig-

nificance of assays for adrenalin content of the glands secured at autopsies, even when reliable methods are employed, is obscured by the fact that adrenalin rapidly disappears from the gland or is altered after death and that infections per se seem to deplete the adrenalin content of the medulla.

We would expect reduced content and output of adrenalin in advanced sclerosis of the gland, but even in this case, in animals, the content and output are found to be in the normal range if age alone is the variable and no infection or disease prevails (52).

The supposed adrenalin factor in diabetes is still without adequate proof, and its alleged factor in hypertension, except when associated with tumor of the medulla, has been fairly well disproven (13, 52). We are, therefore, forced to conclude that valid data as to the ageing process in the medulla, and hence the medullary factor in the general nexus of ageing, are not yet even on the horizon.

It is conceivable that although the function of the adrenal medulla is not indispensable for life or health (62) since it can be removed surgically or its epinephrine secretion suppressed, epinephrine may exercise a role which over long periods may be reflected in the processes concerned with the development and course of senescence.

Epinephrine may be in some way related to mineral metabolism. It has been found that injected epinephrine is capable of modifying the reactions produced by calcium salts. Furthermore, epinephrine may be concerned with the distribution of potassium in the body (4). Thus, there might be postulated a possible functional interrelationship between cortex and medulla, if these observations can be said to represent the activity of physiological quantities of epinephrine.

Constant injection of epinephrine, in physiological quantities, have been found to augment the blood sugar and lactic acid (9). While such quantities as may cause this effect are rapidly destroyed in the circulation, it is conceivable that a prolonged or chronic state of mild hypersecretion (i.e., in the upper physiological range) of epinephrine, might by these effects have an influence on the ageing processes of tissues or organs.

There is evidence that the ordinary secretion of epinephrine may exert an influence on the heart, perhaps on the irritability of heart muscle (62). Quantities of epinephrine corresponding to the amounts secreted physiologically, when introduced at a constant rate can cause hemodynamic effects (12). Whatever the underlying factor may be which gives rise to the development of the so-called sympathicoblastoma or phaeochromacytoma, in these conditions it seems almost certain that paroxysmal hypertension is in some way associated with excess epinephrine production. But we must also consider the possibility of an increase of the adrenalin-like "sympathin" in this condition. In fact, the probable production of adrena-

lin-like chemicals in most, if not all peripheral sympathetic nerve endings, necessarily weakens and questions much of the older work and interpretations anent the role of the adrenal medulla in the cardio-vascular processes in health and disease.

The cortex

The extraordinary metamorphosis (degeneration and regeneration) of the human adrenal cortex the first few months after birth (32, 8) needs no restatement in this chapter. The physiological significance of this is at present unknown, especially since it appears to be absent in the newborn of many of the lower mammals. These profound cortical changes apparently go on hand in hand with the secretion of the life sustaining hormone or hormones, because so far as is known the cortical hormone is as necessary *for health and life in early infancy as in later years; the well known adrenal* apoplexy in the newborn is a fatal condition.

In the healthy experimental animal at least one entire adrenal can be removed without inducing any deficiency symptoms whatsoever. As little as approximately one-twentieth of one gland, or less, if supplied with adequate blood circulation, suffices to maintain life and normal health (50, 51). And in species like the rat, with fragments (sometimes microscopic) of cortical tissue along the abdominal aorta, or elsewhere, the two chief adrenals may be removed without bringing on any recognizable symptoms of Addison's disease. There appear to be no reasons for thinking that the healthy man is not equally well provided with cortical tissue way above his minimal needs. Indeed, accessory cortical tissue is not at all uncommonly found if careful search is made at human autopsies. If this is so, we need not wonder that the cortex may show extensive injury incident on vascular sclerosis, local hemorrhage, systemic and local infections, etc., without recognizable symptoms of cortical deficiency.

While the adrenal cortex is labile to the extent that systemic infections, vitamin deficient diets, removal of the anterior pituitary, etc., induce changes that may signify depressor injuries, the hereditary persistence and resistance of the cortex is apparently great, for frank Addison's disease is much less common than are, for example, diabetes and myxedema in man, and so far as we know, spontaneous Addison's disease is unknown in the lower animals.

The isolation of the life sustaining cortical hormone has been in progress for years. A slight storage of the hormone in all glands so far tested is unquestionable. The hormone appears very unstable under ordinary conditions. The methods of isolation and assay available at present are not sufficiently quantitative to yield data of significance in the assay of the hormone content of the blood or of the cortex itself at different ages.

Owing to the changes in the adrenal cortex induced by such conditions as systemic infections, prolonged asthenia, malnutrition, pituitary gland ablation, etc., the histopathology of the mine run of postmortem adrenal glands is difficult to interpret. But apparently normal (or even hyperplastic!) adrenal cortex has been described in persons past 90 years of age (53).

The most significant fact suggesting an important role of the adrenals in geriatrics is the indispensability of the adrenal cortex for life and health, at all ages (50, 51) (dogs, cats, guinea pigs, rabbits, rats and a few monkeys). That the cortex is related to metabolic processes in the period of senescence is indicated by changes in lipoid content, in the mitochondria, siderophilia and other cytological elements (41, 42, 10), and by the greater deposit of pigment granules in the cortex ("Abnutzungsprodukten"—Landau). The juxtamedullary zone of the cortex has been claimed to be related to gonadal function and has been alleged to be endowed with androgenic qualities.

The adrenals have been supposed to influence, significantly, important oxidative processes in the body; e.g., an influence on the amount and behavior of glutathione in the blood and tissues (66, 16). The relation of the glands to vitamins is not well understood, but it may be significant that the cortex is rich in vitamin C.

Calcium metabolism has been shown to be related to adrenal function, probably through interrelation with the parathyroid (51, 63, 47, 56), this may have a bearing on arterial changes, especially those involving calcification—more important in the smaller arteries and renal arterioles.

Chiefly, in relation to senescence, might be considered the as yet only vaguely known metabolic function of the adrenal cortex; acute, subacute and chronic insufficiency are characterized by changes in the composition of the blood and by pathological manifestations in important organs (50, 51, 6) viz., nervous system, circulatory apparatus, alimentary canal, pancreas, parathyroid and probably hypophysis and other endocrine organs. These indicate a profound "intoxication," which in milder form (i e., probably resulting from chronic functional insufficiency) may represent retention of metabolites or toxic substances which might influence the processes of senescence. Toxic substances have been alleged to have been found in the blood of adrenalectomized animals (1, 36, 48). Changes have been found in the blood leukocytes (67, 18).

Sodium chloride was found to be related to the activity of salivary amylase and also to that of the pancreatic and hepatic diastase; this may be related to the moderate disturbances in carbohydrate metabolism associated with adrenal insufficiency.

Changes in the mineral metabolism, viz. sodium chloride (51, 34), potassium (68) and in the nitrogenous metabolism (51), as well as water

balance, carbohydrate metabolism, etc., have a bearing on the question, although these are but little understood as yet. Probably the alleged influence of the adrenals in cholesterol metabolism (65) has a greater influence on senescence than is recognized.

The subject can include even our vague knowledge of important *interrelationships* between the adrenals and other endocrine glands, especially in regard to growth and other metabolic functions in which the hypophysis, gonads and thyroids participate (probably also the liver and pancreas, at least more indirectly). The singular combination of persistent hypertension and hypertrichiasis (virilism) that may appear in adult women usually associated with an hyperplasia or tumor of the adrenal cortex, suggests that some cortical hormone, rather than the medullary, may operate on the vascular mechanism. Such a view is consistent with the profound and persistent hypotension following cortical ablation. Of course, one must recognize that an adenoma of the adrenal cortex may produce chemicals different from those secreted by the normal gland.

Perhaps the only condition primarily associated with abnormal premature age phenomena is "progeria." In this condition one complete autopsy on record records definite atrophic and sclerotic changes in the adrenals; however, since other endocrine organs, particularly the anterior hypophysis, also showed abnormal changes, the disease cannot be said to be primarily the result of adrenal disease.

The characteristic complex of Addison's disease (disturbance of the K, Na balance, the water balance, and possibly the sugar metabolism, the hypotension, alimentary tract and general body asthenia), irrespective of the primary or secondary character of the several factors, is not clearly established even in very advanced age in man. The fact that high NaCl and a low K ingestion appears to control the major cortical deficiency symptoms in patients as well as in animals fairly well, at least for a time, might be made use of in the asthenias of the aged. Should the asthenia of the aged be amenable to this salt therapy (as a specific rather than a drug), we would have the first clear indication of a cortical involvement in the ageing process. But for the present we must say: *not proved*. And yet, we *hasten to add: the adrenal cortex should nevertheless be included* in any comprehensive experimental attack on the problem of ageing. The gonadotropic cortical factor should also be looked into as to its persistence and role, past the period of active gonad life, and its possible relation to the several growth anomalies at that period.

The Thymus

A hundred years of research on the thymus has built up a fairly complete story of its morphological changes with age, but it has given very

little valid information in regard to the functional significance of these thymus changes for the organism as a whole especially in late adult life Developing from essentially the same embryological anlage as the anterior pituitary, the thyroid and the parathyroids, and being, up to puberty, made up in part of what seems to be glandular epithelium (Hassal corpuscles) the thymus is by most people suspected to have endocrine functions in the usual sense. But hormone production by the thymus is still an open question. Earlier extirpation experiments seemed to indicate some influence of the thymus on growth, particularly on bone and calcium metabolism. But the more recent work of Park and McClure (45) appeared to dispose of that possibility, at least for the dog Riddle reports interference with the production of the egg shell after thymectomy in birds. The onset of a more rapid involution at puberty and the reported delay of this involution by prepubertal castration has suggested some mutual influence between the thymus gland and the gonads. In a recent preliminary communication Gersohn-Cohen (20) report that x-ray destruction on the thymus in very young rats leads to nearly complete atrophy of the testes (and complete sterility) in the male, but is without influence on the ovaries of the female. Retarded growth of the body is given by these authors as one effect of x-raying the thymus.

Possibly the most significant reports in the thymus field in recent years are the several papers by Gudernatch (22), Asher (3), and by Rowntree. These investigators fed or injected variously prepared extracts of the thymus to young rats and to female rats throughout their reproductive cycle and report some stimulation of the rate of growth of the young rats, and in the work of Rowntree, in addition, precocious maturity, somatic and gonadal. The composition of these thymic extracts is not known, but they probably contain peptids, essential amino acids, and possibly glutathione (22). The effects reported may therefore be due to an abundant supply of growth stimulating foods (Andersen) rather than to giving excess thymus hormones. This interpretation seems justified, at least until the reverse of these feeding and injection effects are definitely established by total removal of the thymus in young animals In recent experiments (54) Segaloff and Nelson failed to find any retardation of growth in thymectomized newborn rats, and the same investigators also failed to influence the growth of rats by thymus extracts (thymocrescin).

While a few of the peculiar Hassal corpuscles are reported to persist in the thymus into old age, the greater part of the fetal and prepuberal epithelium of the thymus is replaced by apparently ordinary lymphocytes, beginning at the age of puberty, and from that age on the ups and downs of the thymus appear to parallel that of other lymphoid tissue, as in infections, status lymphaticus, etc.

Thus it would seem, on the basis of fairly consistent cytological findings (23, 24), and in the absence of even definite indications of thymic hormone functions at least past the puberty age, that there is probably no thymus factor in ageing, using the term in our restricted sense. To be sure, complete thymic involution is probably not reached till some somatic ageing processes are under way, but to relate these as cause and effect would be idle speculation, at present. The conception of "sudden death", ("Mors thymica") rather than slow ageing, as related to a persistent, enlarged, or "overactive" thymus, is probably untenable.

From the above it seems clear that for the processes of senescence that make their clear appearance in man from the age of 40 to 50 on, the thymus gland is not even one of the minor prophets in Israel. But the ageing of the thymus itself is a problem of first importance and it may have hitherto unsuspected significance for the organism.

The Pituitary

1. A scientifically valid evaluation, and therefore useful rather than confusing, of the very extensive as well as conflicting literature, clinical and experimental, on the pituitary gland, and especially the anterior lobe, in line with the aims of this volume, seems today almost beyond human capacity. At least one anterior pituitary hormone forms an essential link in growth, and hence in repair, if not in the processes of immunity (which, surely, have growth aspects), presumably at all stages of the life span. The theory that such a hormone is an important regulator in the processes of senescence is almost too tempting to reject, even in the absence of valid evidence in its favor. This same lobe produces other hormones on which the activity, if not the very life of such organs as the ovaries, the testes and the mammary gland depend. The latter organs wane with advancing years. Could we settle relations in nature by logic alone, what is more logical than that this waning of the gonads and the mammary glands is caused by an antecedent hypofunction of the pituitary? Again, the anterior pituitary appears to have in some species, at least, a chemical driving machinery acting on the thyroid, and probably on the hormone production of the adrenal cortex, although in neither case is the pituitary machinery absolutely essential for all the functions of these organs. Slight but gradual failure of the thyroid and adrenal cortex activities in advanced years could very well induce some of the gradual decline in physiological processes known as "normal ageing." No doubt, that horse could pull this cart. But does it? And we have actual evidence that the different hormones of the anterior pituitary may not be secreted at parallel rates; that the production of some of them is, indeed, ruled by different chemical masters; that the output of one may go up while that of another goes down (as

appears to be the case of the growth and the gonadotropic hormones in acromegaly). So we may, logically, call on the pituitary in middle life for excess production of the hormone driving, somehow, in the direction of diabetes. And, presto, we have the increasing incidence of diabetes up to the age period of 50 to 60 years. And, coming even closer to the actual phenomena of senescence, do we not have the apparent premature senility of Simmonds disease with its reported parallel, if not antecedent, atrophy of the anterior pituitary, not to mention the Cushing disease, or syndrome, (including persistent hypertension), with its reported indications of war inside the anterior pituitary hormone family? Considering the histochemical literature on the whole pituitary gland by itself, there is sufficient variety of findings to give comfort to almost any kind of hypothesis, and a mere physiologist is poorly qualified to winnow the chaff from the grains of wheat.

2. Were we permitted to rely on such accounts of the gross and microscopic structure of the presumably "normal" human pituitary from early intrauterine life to ripe old age as those given by Parsons (46), and by Cooper (8), this phase of the pituitary story would seem provisionally simple. According to these authors the eosinophile, the basophile and the neutrophile cells make their appearance from the third month of fetal age on, apparently differentiated from the original nongranular cells. The latter persist, however, in slowly increasing numbers throughout life The eosinophile cells increase in size during childhood. The basophile cells also increase in size, and in later adult years invade both the intermediate and the posterior lobes in considerable numbers. The neutrophiles appear to be most numerous in the pituitary gland of old people Parsons' paper is based on a cytological study of 107 human (male and female) pituitaries, ranging in age from childhood up to 78 years. The gross weight and size of the whole pituitary changes but little in either men or women between the ages of 20 to 80 The average for both sexes is from 0.60 to 0.75 g. In Parsons' series there is a slight decline in pituitary weight in women after 60 and a slight increase in pituitary weight of the men past 40. According to Simmonds (58) data on a very large series (800) of human pituitaries well dispersed as to age, there is on the average a slight decrease in gross pituitary weight both in men and women after the fortieth year of life. But considering the unknown relations between endocrine gland size and rate of hormone output, this is a very precarious foundation for a theory postulating anterior pituitary involution as a causative factor in normal ageing This invasion of the posterior lobe by the basophile cells and the usual increase in the pigmentation in this lobe appear to be the main histochemical feature of ageing in the posterior pituitary.

The invasion of the posterior lobe by the basophile cells has been con-

sidered by Cushing and others as a sign, if not a causal link, in ageing. In Parsons' cases this invasion roughly paralleled the age from 40 on, both in men and women, the invasion being somewhat less extensive in women past 40 who had hypertension. Some increase in the number of the neutrophile cells, and a slight increase in the connective tissue of the anterior pituitary are also described in older people.

Some vacuolization appears in the basophile and the eosinophiles in older people. According to Cooper, the unusually great vascularity of the anterior pituitary attained at puberty is retained until the age of 50 or 60 years, when a slight but progressive diminution of the blood supply of this part of the gland appears to set in.

In the absence of frank pituitary gland disorders (tumors, cysts, etc.), and generalized and excessive vascular sclerosis involving also the pituitary, this gland appears, anatomically and cytologically, remarkably stable from the age of 20 on to 80. We should pause and ponder before ascribing either hypo- or hyperfunction with ageing to this gland on these changes in structure, as we are able to interpret them at present. If, as appears to be the case, the anterior pituitary has differentiated from a common anlage (embryonic pharyngeal epithelium) into a factory producing five or more distinct chemical substances, the relative anatomical stability of the gland is indeed striking, in view of the indications that recent evolutionary achievements tend to be labile.

3. For the present we may consider at least five anterior pituitary hormones as fairly well established, the growth promoting, the gonad stimulating, the mammary gland stimulating, the thyroid stimulating and the substance acting with or via the pancreatic islets in carbohydrate metabolism. However, the evidence for the actual secretion of some of these substances by the gland is both meager and indirect. If there be only four types of cells in the anterior pituitary some of these cells are evidently producing more than one hormone. There appears to be a more or less independent rate of production of these several hormones. At any rate cystic or other types of degeneration of the anterior pituitary may affect the gonadotropic factor primarily, leaving the growth factor, at least, unimpaired, in which case we have sexual infantilism but normal body growth. But gonad involution, or more to the point, castration before or after puberty, appears not to retard the secretion of at least one of the gonadotropic factors (Prolan A). Pregnancy, castration and total thyroidectomy induce some variable (depending in part on species and sex) cytological changes in the anterior lobe. The precise causes and functional consequences of these are still largely conjectural. Since hypothyroidism and hypopituitarism each impair body growth and gonad activity, and since one pituitary hormone stimulates the thyroid, another the gonads, and,

from the castration effects, the thyroid hormone appears to have some (probably stimulating) effect on the pituitary, as well as on the gonads, the possible primaries in this complex are several and still await solution.

In a certain sense, the involution of the human ovaries in late adult life, the gradual reduction in secretion capacity of mammary glands, the more gradual involution of the mammalian testes, are a part of the picture of ageing. In the life of these several organs anterior pituitary hormones form important, if not, indeed, essential links. If the age involution of these organs is primarily a matter of specific hypopituitarism, we definitely should be able to prolong their life span by pituitary hormone therapy. This is, at present, uncertain, but seems a promising line of attack, given controlled materials. In the case of the human female, whether the factor be primarily ovarian or pituitary (or what have you?), the fairly definite timing of the involution in normal women, and the more gradual gonad involution in the human male, points in the direction of sex-linked heredity in gonad ageing

As to growth and repair, pituitary growth hormone, and ageing, except in such special cases as neoplasms, the male prostate (man), local hair follicles in hypertrichosis, and local foci of bone hyperplasia in some types of arthritis, growth and tissue repair slow down with age, although not in strict parallel. This slowing down tends to be marked in advanced old age. The pituitary gland may, indeed, produce more than one growth hormone. The pituitary action on the ovary and the thyroids may be, and is, so interpreted by some. But as to the pituitary influence on the other organs of the body, present evidence indicates only one growth hormone. And there is no clear evidence that the reduction in the rate of production of this hormone is primary in the slowing up of growth and repair with age. Nor is there evidence, except for the special situation of acromegaly, of such excess production of this growth hormone as would account for the increased tendency to neoplastic growth in old people. Special carcinogenic chemicals are, so far, indicated from the gonads, not from the pituitary gland. This Gordian knot is not solved by postulating a primary hereditary factor in neoplastic growth, for heredity does not operate without chemical machinery.

Future work with more accurate quantitative methods of chemical and bio-assay studies of the blood, the urine and the anterior pituitary in controlled populations may disclose variations with age in the hormone output, qualitative and quantitative, not evident from the literature of today. At present, the anterior pituitary seems a relatively stable organ. Such variations in pituitary functions as shown in acromegaly in early adult life and in gigantism in youth, both very probably due to an excess production of the growth hormone, and sexual infantilism and dwarfism of pituitary

to show that excess production of pituitrin by the posterior hypophysis is a factor in the arterial hypertension complex at any age. A new way of testing these possibilities seems to open, by the Goldblatt technique (chronic renal ischemia) of producing chronic arterial hypertension in dogs. Will posterior lobectomy relieve this condition? This does not seem probable, but if it does, we are on the way. According to Page (44) the arterial hypertension of Goldblatt is not maintained after complete extirpation of the adrenal cortex. But, if confirmed, this fact cannot be, at present, ascribed directly to a cortical hormone factor in that form of hypertension, and the fact itself is questioned by recent experiments of Rogoff.

PIGMENTATION. The problem of cell pigmentation (surface and body cells) in the ageing process, and the relation of the posterior pituitary as well as the pars intermedia thereto appears to be a matter of comparative physiology and pathology. We do not think it can be settled on mammals alone. In some of the lower species the posterior hypophysis (and the pars intermedia) seem to influence not only the chromatophores, but also general cell pigmentation. But the mosaic distribution of skin and hair pigmentation is such that no hormone circulating in the blood can be the only primary factor. The ageing white man usually loses the color of his hair (on the scalp only) before he loses the hair itself, while some of the body cells develop more pigment, and the skin becomes darker. If this is hormonal action, it becomes complicated, indeed. As regards the skin of the ageing white man, it seems more probable that the increased pigmentation with time is more a matter of chronic effects of the ultra violet light than a plus or minus hormone action. Perhaps the work of Geiling on the whale pituitary, where two of the pituitary lobes are geographically separated, will bring some light into this perplexing situation.

SUMMARY

In the preceding paragraphs of this chapter we dealt with the problem of endocrine control (dietary, vascular, hormonal, metabolic, nervous) only incidentally. But this question seems so fundamental, especially in the role that decreased or increased hormone production may play in the ageing processes of the other physiological machinery, that this brief space, given to recapitulation and attempts at greater clarification, may be useful.

1. In the matter of food factors, the fact that the thyroid glands depend on iodine and the gonads on vitamin E seems well established, and in the case of the iodine-thyroid relation, the mechanism appears as simple as that of iron to erythropoiesis. Several endocrines (thyroid, gonads, adrenals) exhibit cytological and probably functional changes in general starvation (Jackson). High caloric diets seem to put a "strain," probably via increased hormone production, on the islets and the thyroids, especially

by high carbohydrate intake in the former, and by high protein in the latter. The phenomena themselves need further study, especially in the comparative field, in search for the causal steps.

2. The dependence (within limits) of the rate of hormone output on the vascularity of the specific endocrines seems both reasonable and probable, but, so far, this dependence rests largely on assumptions, such as the usual increased vascularity in the hyperplastic endocrine gland; the periodic increase in the vascularity of the gonads, parallel with periods of increased hormone secretion; the dependence of urine output, muscle contraction, cardio efficiency, etc., on the blood flow through these respective organs, etc. But to what extent the ordinary vaso-motor mechanisms of the endocrines indirectly modify hormone production is still unknown. Nor do we know how great a reduction in local vascularity must be induced before hormone output is decreased. In the case of the liver (in cirrhosis, fatty infiltration, etc.) we have an example of the danger of reasoning "on general principles," in the absence of actual tests. The attempts to control hyperthyroidism in man by partial ligation of the thyroid arteries have been less successful than one had a right to anticipate on theoretical grounds. So this virgin field invites invasion via the experimental route. Until experimental and observational data on this aspect of hormone output control are at hand, speculations anent the influence of endocrine sclerosis on the rate of endocrine function may be interesting, and even true, but they are not science.

3. The matter of mutual control among the endocrines presents fundamental but extremely complicated questions for solution. The influence of the thyroid hormone and at least one anterior pituitary hormone on the gonads may be on metabolism and growth rather than on gonadal hormone output, as seems to be the case with the anterior pituitary influence on the mammary gland. The influence of the gonadal hormones on at least one of the anterior pituitary hormone factories appears to be inhibitory rather than stimulatory. The temporary influence of the anterior pituitary on the thyroid gland appears to be both on gland growth and hormone output. The apparent influence of some anterior pituitary factor on the carbohydrate metabolism may be on organs other than the islets, for it operates in the absence of the pancreas. Evidently, we are here concerned either with a pancreas factor keeping some process in the anterior pituitary in check, or else with some type of balancing action by insulin and the pituitary factor in the liver, the muscles and possibly other organs. The factual interpretation, as regards hormone production, of the several cytological changes induced in several endocrines by total ablation or total atrophy of any one of these glands constitutes a major research task of tomorrow.

4. The easy and plausible assumption that the rate of the hormone output in general is controlled by the involuntary nervous system via direct secretory nerves, and action on these nerves by such substances as adrenalin, sympathin, etc., has acted as a soporific rather than as a spur, in some quarters. Should this assumption turn out to be superficial and essentially incorrect, it will look worse than foolish. What appears to be true secretory nerve control, in the case of the endocrines, has been made out for the adrenal medulla-adrenalin alone. And in this case we have the additional and curious fact that when these secretory nerves are severed from the central nervous system the medulla no longer puts out adrenalin. So here we have not only secretory nerve control, but, apparently, exclusive nerve control. However, the medulla does not seem to atrophy after such denervation. It is precisely this nerve control of adrenalin secretion and the stimulation by adrenalin (in a certain concentration) in sympathetic nerve endings in general that has made the assumption of sympathetic nerve control of all the endocrines so alluring to some colleagues.

The search for such secretory nerve mechanism has centered mainly on the thyroid gland. Here Cannon and his collaborators have reported data from many ingenious experiments, data consistent with but not proving secretory innervation of this gland. More recently Cannon (5) has reported that total, or nearly total sympathectomy (in the cat), does not lower the B.M.R., showing that even if secretory nerves to the thyroid gland are present, the essential drive of even this gland is in this species directly chemical. And since total sympathectomy induces no sequelae referable to hypofunction of any of the other endocrines, the chemical control appears to hold for all of them, except the adrenal medulla and possibly the anterior pituitary, as the nerve-path collecting the anterior pituitary and the hypothalamus remains intact in the Cannon experiment. But important as these findings are, they do not dispose of the question of endocrine secretory nerve control, for it is well known that the normal gastric glands, after section of both vagi nerves, secrete enough gastric juice to meet the digestive needs of the animal, and yet we know that the vagi carry secretory nerve fibers to the gastric glands. This question seems particularly pertinent for the endocrine phase of the ageing problem, since instability in the nervous machinery is part of the ageing process, and if we have nerve control of hormone output, disturbance of this control in the aged is, at least, a probability. And, finally, no one can critically examine the difficult literature on the endocrines in senescence without being disturbed by the indications of at least quantitative differences in the control mechanisms and in the resistance and persistence of

the endocrines, not only in different species, but also with sex. Until these variations are cleared up as to cause (hereditary or environmental), we will continue to commit sins against science, especially in our generalizations in this field.

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16

CYTOLOGICAL CHANGES IN THE CELLS OF THE PITUITARY, THYROIDS, ADRENALS AND SEX GLANDS OF AGEING FOWL

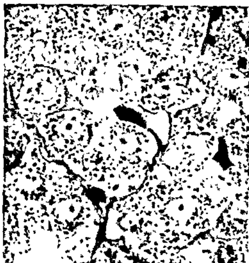
FERNANDUS PAYNE

Bloomington

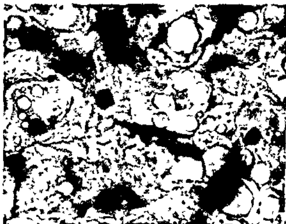
The present chapter will be limited to descriptions of changes which occur in the secretory cells of the pituitary, thyroids, adrenals, and sex glands of ageing fowl, followed by a comparison with changes under certain experimental conditions and a brief discussion of the possible significance of these changes.

The life histories of fowl are none too well known. Genetically they have been crossed, recrossed and inbred. The many varieties differ not only morphologically but in many other ways, such as rate of growth, breeding habits, age of sexual maturity, laying capacity and length of life. There is much variation even within a single variety with respect to all these factors, and food and environment play important roles in all of them. As an example of this variation I cite a study made by Goodale (14) on 297 White Leghorn pullets each of which laid 300 eggs during the first year. He reported that the average age at the time of the first egg was 172.3 days. The range, however, was from 149 to 225 days. While the group was highly selected, other non-selected White Leghorn groups would probably fall near these figures.

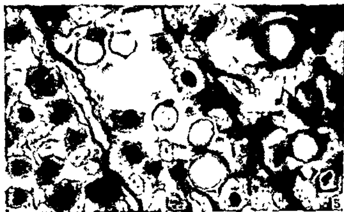
Generally speaking, hens lay the greatest number of eggs the first laying year, following which production declines. The time of the last egg is highly variable, and I have no extensive data on this question. One hen in my collection, age 9 years and 45 days, laid a few eggs the month before she was killed. Another hen, 10 years and 44 days old, had not laid for ten months before she was sacrificed. Even these two records demonstrate that White Leghorn hens may continue to lay up to 9 years of age.











Figs. 1 to 5

While there are older records, these must be above the average as many hens cease to lay before 9 years. Of course, only a few ever reach such an age. Breeders usually discard hens after the first year of laying because of the decline in productivity, and disease takes a high toll.

Cockerels mature somewhat earlier than pullets, but I have no precise data. Cocks are usually discarded by breeders after the first year of service because of some degree of sterility. While I do not know the cause of sterility at this early period, it probably is associated with a lessened sperm supply. Neither do I know the upper age limits for fertility in males, but in a 9 year old Rhode Island Red male in my collection no sperm were present in the testes.

The Pituitary

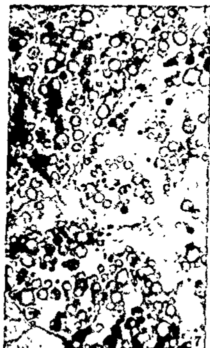
The number of different kinds of secretory cells in the fowl pituitary is still an open question. Six can be easily identified: basophiles, two kinds of acidophiles, chromophobes, broody cells and thyroidectomy cells.

Ageing changes occur in acidophiles, basophiles and to some degree in chromophobes (5, 6). Mitochondria within the basophiles are granular in appearance and irregularly distributed throughout the cytoplasm (fig. 1). At times there may be some concentration near the nucleus. As early as 65 days of age in the male, modified mitochondria may be seen in an occasional basophilic cell. The first visible change is an enlargement of some of the mitochondrial granules (fig. 2). Increase in size is followed by the formation of what appear to be vesicles which may be spherical or irregular in shape (fig. 3). The vesicle-like structures consist of two different substances, an outer peripheral layer, relatively thin, which stains red with acid fuchsin, and an inner central region which takes on a golden orange color when the acid fuchsin is destained with picric acid. In unstained, osmic-treated material, the peripheral layer is black, while the central region is opaque, glass-like and may be slightly orange in color.

As age progresses, more cells and more mitochondria become involved. The vesicle-like bodies grow and fuse to form larger bodies, but the extent of the increase and fusion is variable, as well as the number of cells involved. Fusion may continue until only a few bodies (fig. 4) or even only a single large body is present in a given cell (figs. 5 and 6). Following more extreme modifications, cytoplasm and nuclei are eventually destroyed, leaving the bodies lying in intercellular spaces (fig. 7). Figures (figs. 1–7)

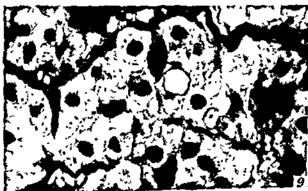
Figs. 1 to 5. These figures illustrate mitochondrial changes in the basophiles













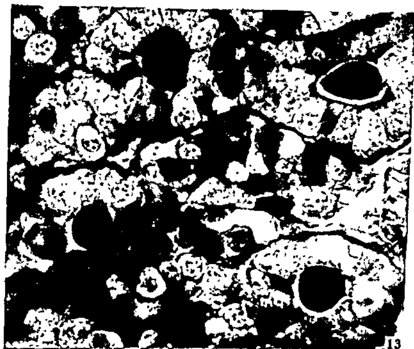
Figs. 6 to 11

give a better idea of these changes than descriptive words. In males of 5 to 9 years of age mitochondrial changes may be in progress in as many as 50 per cent of all basophiles. The remaining basophiles undergo changes of a different character. They recede in size and become much smaller cells than the large functional basophiles of a cock or hen at the peak of reproductive activity. The nuclei of most of them are pycnotic and the general appearance is that of non-functional cells (fig. 9). The result of both these kinds of basophilic changes is a pituitary in which only a few, if any, basophiles are functional and hence a pituitary in which but little gonadotropic hormone can be produced. The pituitary from a Rhode Island Red male, 9 years old, the oldest in my collection, is such a pituitary.

Paralleling, if not caused by the lessened supply of gonadotropic hormone which must accompany basophilic degeneration in ageing male fowl, is the decline in sperm production and finally the degeneration of the testes. Reduction in sperm formation can be observed at 6 years of age in White Leghorns and at 5 years in Rhode Island Reds and probably begins much earlier. Following these ages the change is gradual. Sperm formation had ceased entirely in a 9 year old Rhode Island Red. In this same bird the testes were small and degenerate, the walls separating the cords having largely disappeared.

The changes which I have described in the mitochondria of basophiles of male fowl are not found in the basophiles of pituitaries which I have examined from female fowl up to 10 years of age. They were present in 1 or 2 females 13 years old. I have no material in the range from 10 to 13 years, and nothing beyond 13 years, but this age must be close to the upper limit of the life span. In these 2 old females, however, there were no functional basophiles. Cells, in which mitochondrial changes had not occurred, had undergone the second type of change in which the cytoplasm and nuclei shrink in size and become pycnotic. The cells were more degenerate than in any males examined and had none of the appearances of active functional cells.





FIGS. 12 AND 13

FIG. 12. Thyroid follicle almost filled with cells by proliferation from within. From a 5 year old Rhode Island Red male. × 720.

FIG. 13. Acini in pituitary of 6 year old female. × 1600.

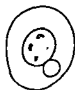
Mitochondrial changes, similar to those described for basophiles, have been observed in chromophobes.

Ageing changes in acidophiles are not so pronounced as in basophiles Acidophiles with secretory granules never completely disappear in either male or female, but in old age they are fewer in number. They shrink in size and the granules which remain stain much darker than in active functional cells. For the most part nuclei are small and pycnotic. Lying in the cytoplasm of each of these modified acidophiles is a single spherical body, somewhat variable, which approaches the nucleus in size. Usually these bodies are uniformly clear throughout (figs. 10 and 17) but occasionally the periphery may stain red as it does in the basophilic spheres (fig 16). Their origin has long been in doubt but now the evidence indicates that they arise by the fusion of smaller spheres (fig. 36) which in turn arise from mitochondria.

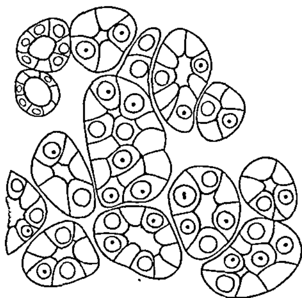
Cells in pituitaries of young fowl are arranged in irregular solid cords separated by thin membranes. Between 2 and 3 years of age cavities or acini appear within some of the cords. Cells, including both acidophiles and basophiles, become rearranged, often in a single layer, giving the impression of follicles (fig. 13). Colloid from some source fills the cavities, but it is questionable whether it is secreted by the surrounding cells, as they show no signs of activity. These acini increase in number with age. Small pigment-like granules of mitochondrial origin are often aggregated in the central ends of the acinar cells. They are especially prominent before cavities are formed (fig. 8).

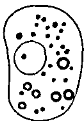
The Thyroid

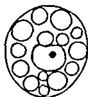
At all ages there is much variation in the size of the thyroid, the size and number of follicles and in the height and secretory activity of the cells of the follicles. The two glands within the same individual are usually different. Material of a colloidal nature is always present in the follicles. Five days post-hatching, the thyroid is small with few follicles, which are also small. The cells, on the other hand, are relatively large and are variable in size and height. One, two or more large cells in each follicle stand out as much larger than all the others (figs. 37 and 38). These large cells divide and the daughter cells continue to divide, thus adding to the number of cells in the follicle. Probably other cells also divide but division figures are rarely observed. The result is a follicle with large columnar cells in one region while the remaining cells are cuboidal or slightly flat. As division continues, the differences in cell size disappear but may reappear with periods of increased secretory activity. Up to 60 days, plus or minus, all cells are either cuboidal or columnar, following which, cells of follicles in the center of the gland gradually decrease in height, and finally in glands

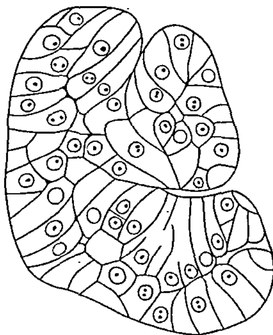

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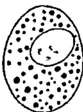

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Figs. 14 to 20

of 130 days and older all central cells may be flat. There are always some follicles at the periphery, however, in which the cells remain columnar and active. In general the colloid in the central follicles stains red with acid fuchsin methyl green while the colloid in the peripheral follicles stains green. These colors are probably indicative of chemical differences within the colloid.

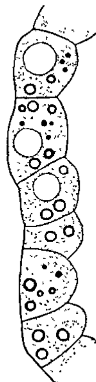
Briefly these statements give an outline of the development of thyroid glands in control fowl up to the time of sexual maturity and are necessary for an understanding of what follows.

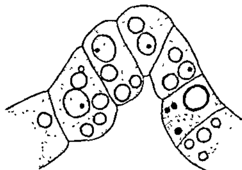
A number of definite ageing changes have been recognized in our study of thyroids of ageing fowl. They begin at different times in different individuals and run concurrently, but when they first begin is impossible to say. In one White Leghorn male 2+ years old, changes had already made considerable progress, but this individual was an extreme variant. The most highly modified gland was taken from a 5+ year old Rhode Island Red male. An obvious change is the reduced size of the thyroid, which in extreme cases may be no larger than that of a 20 day chick. Within the gland changes are even more marked. The follicles become smaller and fewer in number and the distribution of the large and small follicles is more irregular. Colloid is present in all follicles, regardless of size, but the staining reaction is more variable in old than in young fowl. Even in the same follicle the central area may stain red while the peripheral region adjacent to the cells may stain green, following acid fuchsin methyl green. In those glands most affected by ageing changes the colloid may appear as irregular flocculent masses. The appearance is that of degeneration. While secretory activity is greatly reduced, it never ceases entirely in all follicles. This is not only indicated by the height of the cells but also by the presence of secretory droplets within the cells and by the color of the colloid which stains green in those follicles where activity continues.

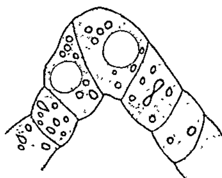
In thyroids of old fowl may be found one or more modified areas in which the follicles are variable in size but for the most part small (fig.

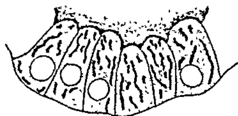
Fig 14 An area of modified follicles in the thyroid of a 6 year old Rhode Island Red female. × 720.

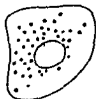
philes. × 1600.

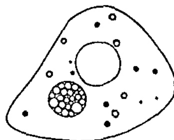

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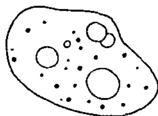

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FIGS. 21 TO 27

14). *Colloid* always stains green, never red. Cells which are large assume the appearance of cells in young active thyroids. Distinct follicles may even be destroyed, leaving masses of large irregularly shaped cells, with occasional colloid areas between them (figs. 15 and 28). There are no limiting membranes surrounding these areas. As they grow, they seem, by means of pressure, to push aside adjacent follicles.

Follicles in which there is cell proliferation into the central colloid area may be found in old fowl. Sometimes the colloid is completely replaced by cells most or all of which are degenerate (fig. 12).

Mitochondria in the follicular epithelium of young fowl are usually filamentous in character (fig. 21) but may sometimes be spherical. For the most part the threads appear to be continuous and uniform throughout, but of different lengths. Occasionally there are indications of definite units arranged end to end. In old fowl filaments are replaced in most follicles by spheres which change into spherical bodies much like those described in the basophiles of pituitaries. These modified mitochondria are variable in size and are larger in Rhode Island Reds than in White Leghorns (compare figs. 22 and 23). My information is still too meager to speak with certainty, but it indicates that changes in males occur earlier and progress more rapidly than in females. At least, the most highly modified mitochondria have been found in a Rhode Island Red male of 5 years and 4 months of age (fig. 42). Females studied ranged up to 10 years old.

The Adrenal

Cytological changes in the adrenal glands of fowl are more difficult to describe and to correlate with physiological changes than are the changes in the pituitary and thyroid. Medullary and cortical cells are clustered in island or strand-like irregular masses with the masses intermingled in patchwork fashion. There is no layer arrangement as in mammals, although neither the medullary nor cortical cells are the same throughout the gland.

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months old. Note large bodies similar to those of basophiles of pituitary. Compare with photomicrograph, fig 42. × 1600.

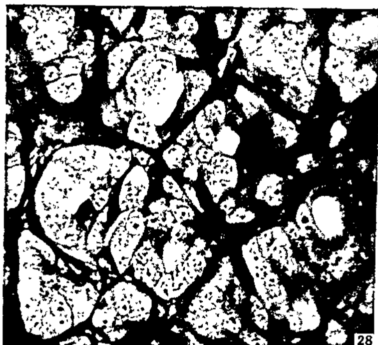
FIG. 23. Similar to fig. 22 but from a White Leghorn female 6 years old Bodies not as large as in fig. 22. × 1600.

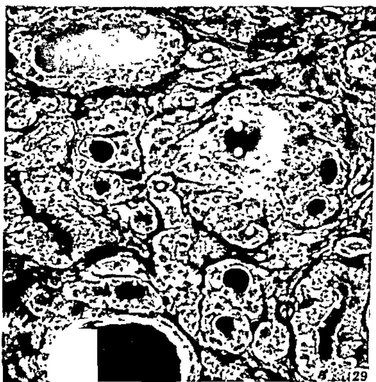
FIG 24. Mitochondria undergoing changes in a 60 day runt × 1600.

FIG 25 An inactive medullary cell showing granular mitochondria and pycnotic nucleus × 1600

FIG. 26. A medullary cell from a Rhode Island Red female, 7 years old Note large body formed by fusion of mitochondrial vesicles. This is the same cell as in photomicrograph, fig. 11. × 1600.

FIG 27. *A medullary cell from adrenal of* White Leghorn female, 9 years 4 months and 8 days old Mitochondria are changing to small vesicle-like bodies which fuse to form large body as in fig. 26. × 1600





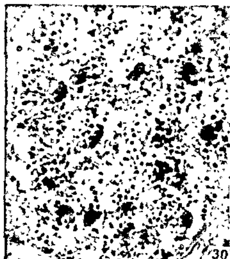
FIGS. 28 AND 29

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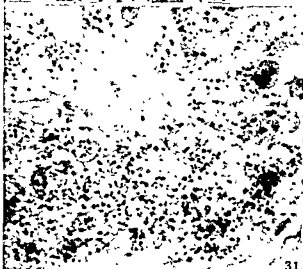
Peripheral cortical cells are relatively small and free of secretory droplets in young chicks up to 20 days or even older. These cells, during the height of secretory activity, become much elongated and filled with droplets. Cell walls may become indistinct and seem to disappear. Beneath the periphery lies a second region of cortical cells, some of which are filled with secretory droplets. Others with cytoplasm and nuclei much reduced in size have the appearance of cells in process of degeneration. Whether they are actually degenerating or whether they are undergoing regressive changes with the liberation of secretory materials is questionable. My own interpretation for the moment is the latter, because in this same region cells can also be found free of droplets, in which the cytoplasm and nuclei have again regained their normal size and appearance (fig. 41). There may be some degeneration but it is much less than a superficial study would lead one to believe. As with the cells of the pituitary, there is much plasticity and change in morphological appearance with change in physiological activity. In the central region of the adrenal the cortical cells are still different. Some, as in region two, may show signs of degeneration. Most are cells with large spherical nuclei and with cytoplasm filled with secretory droplets. The cytoplasm and droplets, however, do not have the same appearance as in regions one and two, nor do they react in the same way to stains. Judging from appearances, I am inclined to suggest a different function for these inner cells. While I have described the cortical cells as arranged in three regions, there are no lines of demarcation.

The medullary cells at the periphery of the adrenal are small and probably are the primitive type cells from which functional medullary cells arise. They have some of the characteristics of small ganglionic-like cells which lie within the adrenal ganglion. Beneath the peripheral region, which is not well defined, the medullary cells are of the functional type with the exception of a few small cells which appear to have little or no cytoplasm (fig. 40). Most medullary cells are in a state of inactivity, and the cytoplasm, in which no secretory droplets are visible, stains dark green with methyl green while the nuclei, which are small and pycnotic, stain red with acid fuchsin (fig. 25). Other medullary cells, fewer in number, stain lightly or not at all. The nuclei are clear and spherical. These cells are either actively secreting or discharging or possibly both.

A few definite and significant changes are observable in the adrenals of ageing fowl. The glands become much reduced in size, due in part to shrinkage of cells, but also, in part, to degeneration of cells. There is much variation, but in hens from 5 to 10 years of age, secretory activity is much reduced. In the glands most extremely modified there can be little activity, but as far as my observations go, activity had not ceased entirely in either cortical or medullary cells.

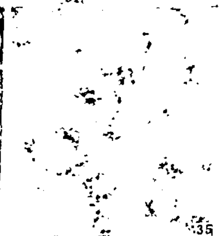












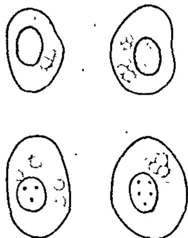
Figs. 30 to 35

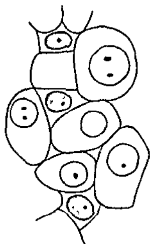
The most striking modifications, other than degeneration, occur within the mitochondria. Mitochondria in the peripheral cortical cells of young chicks, before accumulation of secretory droplets, appear usually as variable size spheres which stain uniformly (fig. 20). Within these same cells, but more often in cells after secretory activity has begun, mitochondria may appear as small rings or circles due to differential staining (fig. 30). Within these spherical mitochondria are granules, variable in number and size. The number of granules is more often 1, 2, 3 or 4, but larger numbers are frequent. When destaining is carried to extremes, the spherical character of the mitochondria may be lost, leaving only the granules (fig. 31) Further details with respect to mitochondrial behavior will be reserved for another paper.

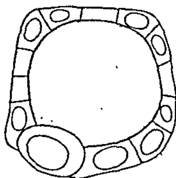
The first ageing change in the mitochondria of the cortical cells is the loss of capacity to stain with acid fuchsin. They appear as brown pigment-like bodies and have been observed in a White Leghorn male as early as 2 years and 4 months old. The granules may still be present, but disappear with advancing age. The mitochondria become larger, and are often vacuolated. Fusion may occur forming large bodies (fig. 32).

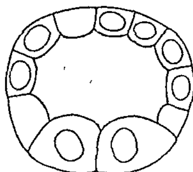
Mitochondria of the medullary cells are irregularly shaped granules and not spheres (fig. 25). They stain uniformly and show no indications of an internal structure. With age they change much as do the mitochondria of the basophiles of the pituitary with the exception that the peripheral ring is less pronounced (fig. 27). The central region has the same golden color. The individual mitochondria fuse, forming eventually a large body of near nuclear size (figs. 11 and 26).

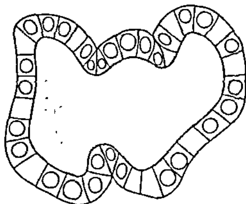
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ganglion, which is large in fowl, is usually separated from the adrenal by connective tissue, but the membrane may be absent in places, leaving the ganglionic cells continuous with the peripheral medullary cells. Within the ganglion the ganglionic-like cells intergrade between the small neuroglia

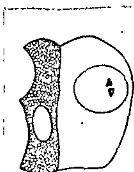












Figs. 36 to 41

and the large ganglionic cells and may arise from the neuroglia cells. Their nuclear structure is similar to that of the ganglionic cells. In some ageing fowl these ganglionic-like cells, when in contact with the medullary, increase in number and the mass, wedge-like, seems to push its way centralward into the adrenal (fig. 44). Several of these growths may be found in a single adrenal. Whether the cells increase in number wholly by division, by differentiation from neuroglia cells, or whether they differentiate in part from the small cells previously mentioned, which lie among the medullary cells, is uncertain. Cells in division are rarely seen. Further study is needed, not only as to origin but also as to significance. The masses of cells and their penetration of adrenal tissue have some of the appearances of tumors.

The Gonads

Ovarian changes have not been followed. We know, however, that after the first year of egg production, the number of eggs laid per year declines gradually and may cease entirely about nine years, plus or minus. Testicular changes follow a somewhat similar path. Sperm formation had ceased entirely in a 9 year old Rhode Island Red cock and the testes had undergone considerable degeneration.

Castration, Thyroidectomy, Hypophysectomy

Removal of the testes in fowl brings about certain well known changes in the pituitary. The pituitary itself enlarges. The basophiles increase in size and number and the acidophiles decrease in number. Mitochondrial changes in the basophiles are similar to those in controls but more marked (fig. 7). Capons 4 to 6 years old show greater changes than cocks 9 years of age. Pituitaries of control females, which show no mitochondrial modifications in the basophiles up to 10 years of age, behave as capon pituitaries when the left ovary is removed. Assays of control and castrate pituitaries by Breneman (2) demonstrate the presence of larger amounts of gonadotropic hormone in pituitaries from castrates. The effects of castration upon the thyroids and adrenals I am not prepared to discuss at this time.

Following thyroidectomy in young chicks 3 to 5 days old and sacrificed

[illegible]

returning to a state of activity. X 1000.

rate of comb growth varies with the quantity of androgen present (Breneman, 2). Turner and Kempster (8) have produced evidence that egg production may be increased by thyroxin feeding and Bisonnette (1) has demonstrated the effects of increased gonadotropins in starlings by lengthening the daylight period. Pieces of testicular tissue are sometimes left when castration is performed. Such pieces may regenerate and secrete hormones, yet the pituitary in those fowl in which the regenerated pieces remain small is similar to that of a capon. Of course, a certain threshold of androgen secretion may be necessary before there can be prohibition of castrate changes in the basophiles. That a certain threshold is necessary *is indicated in some recent experiments of Breneman and Mason (3) in* which they injected daily doses of 10 gamma of testosterone in young capons from the tenth to the thirty-ninth days. At 40 days combs were larger than in controls, but the pituitary was that of a capon. The low dosage of androgen did not prevent pituitary changes characteristic of capons. When injections of 50 gamma of testosterone per day were given, however, combs were much larger than in controls, but pituitaries were smaller and the basophiles were inactive. Castrate changes in the pituitary were completely blocked.

I have described some of the more pronounced effects of one gland upon another as approached by gland removal. Following castration the activity of the secretory cells of the pituitary is greatly modified. Basophilic activity is increased; acidophilic activity decreased. After the removal of the thyroid, the pituitary is again changed, but in a reverse manner. Basophilic activity is reduced by failure of the cells to develop while acidophilic activity remains high as judged by the number of cells filled with granules. Due to an insufficiency of gonadotropic hormones from the pituitary, the sex glands do not develop. Lack of thyroid hormone also causes degeneration of the cortical cells of the adrenals.

Hypophysectomy is followed by changes in the gonads, thyroids and adrenals. Gonads either remain juvenile or regress, depending upon age at the time of operation. Such changes are not much different from those following thyroidectomy. The thyroids remain small and, while there is variation, the cells are for the most part cuboidal when hypophysectomy is performed at 50 to 60 days. When performed at 1 to 2 years on hens, the thyroid may become a degenerate structure somewhat similar to the thyroids of old fowl. Not only do follicles and cells change but the colloid no longer stains uniformly, indicating chemical change. There may be large areas of small follicles (fig. 29) which arise in part by constriction of follicle walls and also in part from interfollicular cells. Many if not all cortical cells of the adrenal degenerate.

Certain of these changes in the gonads, thyroids and adrenals are similar to ageing changes in these same glands. Since the evidence clearly points to a decline in pituitary hormone secretions in old fowl, and since pituitary removal eliminates all pituitary hormones, it seems logical to suggest at any rate that the absence of pituitary hormones on the one hand and a decrease in quantity on the other may bring about similar changes.

Granted that hormone output is reduced in aged fowl; that a change in the output of one gland may affect the activity of other glands; and that these changes affect metabolic activities throughout the organism, what are the inferences to be drawn concerning the relationship of the ageing changes I have described and ageing and death? Is the decline in secretory activity of the endocrine glands causal or does the decline merely parallel changes elsewhere? Even if we grant that changes are causal to some degree, and no one can say they are not, we still are faced with the question, what initiates the changes in the endocrine gland or glands which starts the decline in hormone secretion? While we wait for crucial experimental data, it is hoped that observations on the endocrine glands of fowl, such as I have recorded, may add one more small link in the chain of cumulative evidence pointing toward the solution of the problems of ageing.

Aside from the marked decline in hormone output in old fowl, the most interesting observations pertain to mitochondria. In the basophiles and acidophiles of the pituitary, the follicular cells of the thyroid and in the cortical and medullary cells of the adrenal, mitochondria may become modified as previously described into spherical or irregularly shaped bodies, increase in size and fuse. The end result in the basophiles may be the complete destruction of cells. Possibly these changes may be nothing more than degenerative changes. Even if they are degenerative changes why should they begin as early as 65 days in male fowl and why should they progress more rapidly in capons? Why should changes in the hen be delayed until after 10 years of age and why when the functional ovary is removed should these changes be similar to those in capons? If we only knew the function of mitochondria we might guess a little more intelligently. Are they in any way concerned with metabolic processes, which we know decline with age? If so could there be a causal relationship? With respect to mitochondrial changes in the basophiles, the presence or absence of androgens and estrogens apparently makes a difference. In the presence of androgens or in the absence of both androgens and estrogens, changes occur while in the presence of estrogens they do not occur. In the 1 hen 13 years old in which mitochondrial changes were observed, estrogen was probably absent, unless it had its origin from some source other than the ovary. At any rate the pituitary showed no signs of activity.

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17

HOMEOSTATIC AND HISTOCHEMICAL ASPECTS OF THE ENDOCRINE GLANDS

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The subject of endocrinology is commonly regarded as beginning with the lecture of Brown-Sequard before the French Academy of Medicine in 1889. On this occasion, the aged and venerable doctor described how, after self-injection with a testicular extract, the infirmities of age had fallen away and a physiological rejuvenation had taken place. Thus, endocrinology was born as an example of gerontotherapy. It is not surprising, therefore, that students of ageing have constantly kept an eye upon the expanding field of endocrinology, nor that endocrinologists have hoped to find the fountain of youth among the myriad extracts and preparations containing the ever more active principles of the endocrine glands. This search, however, like Ponce de Leon's, has proved fruitless. It appears, from our expanding knowledge, that many processes are altered during physiological ageing, and that restitution of the hormonal balance characteristic of youth may merely restore one of a set of altered mechanisms. Nevertheless, something may be gained by substitution therapy. An old automobile's performance may be improved by a new carburetor. In any event, study of the endocrine changes associated with ageing can lead only to accurate knowledge without which no rational therapy, gerontological or other, can be conceived.

The literature of endocrinology abounds with references to postulated associations between endocrine status and ageing. To date, these postulations have not proved too helpful. Some improvement can be noted in aged people to whom the sex hormones are administered, but equal improvement usually follows psychological counselling or social rehabilitation. It now appears that the endocrine alterations associated with ageing are complex rather than simple. The capacity of the endocrine system to

engage in a shifting balance and its capacity to respond to stress seem to be of more importance in ageing than is any single deficiency.

It is not the purpose of this review to discuss in detail the endocrine changes associated with ageing. This subject has been reviewed elsewhere (1) and certain aspects of it are dealt with in other chapters in the present volume. Rather, the scope of this article has been restricted to some of the homeostatic aspects of endocrine function concerned in the complex physiological readjustments taking place with ageing and to the methods, chiefly histochemical, which have recently proved useful for evaluating endocrine changes in altered physiological situations.

ENDOCRINE ASPECTS OF HOMEOSTASIS

It is significant that the field of endocrinology developed *pari passu* with the elaboration of the concept of homeostasis. Claude Bernard's (2) original enunciation of the principle of constancy of the internal environment depended largely upon his observation that the blood sugar concentration fluctuated only between narrow limits. The mechanisms for regulating blood glucose are largely endocrine in nature—the internal secretions of the islets of Langerhans, the pituitary, the adrenal cortex and medulla. Bernard's concept was elaborated by Cannon who perceived that internal readjustments normally compensated for the stresses and strains of ordinary life, but that in some situations of acute emergency, purposeful deviations from the normal homeostatic balance were permitted. This elaboration of the concept of *homeostasis* was the result of Cannon's study of the secretions of the adrenal medulla, the hormone from which participated in bringing about the response to many of the emergency situations. The modern expansion of endocrinology has been carried out in the light of the concept that hormones act as agents for regulating body processes in such a way that the internal environment is maintained constant, or permitted to deviate only between the prescribed limits suitable for life and bodily activity. Thus, hormones have come to be regarded as one of the principal homeostatic effector systems.

This preoccupation with the metabolic aspects of hormones has caused endocrinology to neglect many situations which otherwise fall within the scope of the field. Glucose is produced from the liver's glycogen stores, is transported to other parts of the body via the blood and there exerts its effect. Secretin and cholecystokinin are produced in the intestine, circulated to the pancreas and gall-bladder, respectively, and act upon secretory and discharge processes in these end-organs. Carbon dioxide and acetylcholine meet certain of the definitions of hormones. Yet, the subject matter of endocrinology usually is restricted arbitrarily to the

hormonal aspects of the gonads, adrenal glands, pancreatic islets, parathyroid, thyroid and pituitary glands.

Hormones may be grouped into three categories, each characterized by the type of regulation exhibited. The first category comprises the hormones of the parathyroid gland, the pancreatic islets and the glomerulosal zone of the adrenal cortex. These glands appear to be regulated in some direct way by the processes which they control. They continue to function adequately after denervation or after removal of the pituitary gland. Parathormone, the active principle of the parathyroid gland, causes the serum calcium to rise; conversely, loss of calcium such as occurs in some renal diseases is associated with hyperplasia and over-activity of the gland. Injections of insulin from the pancreatic islets lowers the blood sugar, whereas hyperglycemia stimulates such an excessive production of hormone that, if long continued, exhaustion and death of the islet cells occurs. Similarly, the salt-regulating principle of the adrenal glomerulosa causes the retention of sodium by the kidney, and elevation of the blood sodium leads to a disuse atrophy of the gland.

The second category contains the hormones of the posterior pituitary gland and the adrenal medulla. Embryologically, these glands develop from neural ectoderm. They maintain extensive connections with the autonomic nervous system throughout life. They are activated by these nervous connections so that the neural and endocrine factors are intimately related.

The third category is composed of a group of endocrine factors centering around the anterior lobe of the pituitary gland. The pituitary produces a number of hormones (thyrotropin, adrenotropin, gonadotropins, and lactogenic hormone) which are necessary for maintaining the structure and function of the thyroid, adrenal and sex organs. In turn, hormones produced in the end organs react back upon the anterior pituitary gland and control its production of the tropic hormones. This group of endocrine factors thus constitutes a self-regulating system.

The hormones of the first category apparently respond in a "dead-beat" fashion to their respective stimuli. That is, the rate of secretion is accelerated or depressed directly by the fluctuations of the end process. On the other hand, the type of regulation involved in the second and third categories is indirect. Stimulation of the adrenal medulla is accomplished only by activity in the intermediary nervous system, and alterations in the rate of secretion of thyroid hormone imply similar fluctuations in the activity of the anterior pituitary gland. With this indirect type of regulation manifold stimuli may compete for, or interact in, the intermediary center which discharges as the final common path to the secretory gland.

In consequence of this intermediation, the adrenal medulla may respond in rage, in hypotension, or in hypoglycemia, and in seasonal animals light or temperature may serve as the exciting agent for stimulation of the gonads. Moreover, inhibition may occur in such systems as is exemplified by the cessation of gonadotropic activity in malnutrition. The "dead-beat" character of the first category adjusts the secretory processes directly to the end process; whereas, the second and third categories permit the integration of stimuli so that the end process may be adjusted to a point appropriate for the activity of the whole organism.

The majority of endocrine experiments have been designed to test simple end organ responses to the various hormones. A multiplicity of such responses has been described. From the data accumulated by such methods it has become apparent that complex physiological mechanisms regulate the active concentrations of the various hormonal factors. The question arises as to whether each of these endocrine factors is a physiologically independent unit capable of variations without affecting the activity of the other factors, or whether some or all exhibit physiological linkages such that varying one item leads to a corresponding readjustment of others until the entire constellation achieves a new quantitative interrelationship.

At this point a related topic should be introduced. For many years, endocrinologists have debated the question of the master hormone of the pituitary gland. Cytologically, the pituitary contains two principle types of secreting cells, the acidophiles and the basophiles. It has been suggested, therefore, that only two hormones, one from each type of cell, should be elaborated by the gland. This point of view has received some support from clinical observations, since in acromegaly, a type of pituitary disease involving the acidophiles, symptoms are present which involve the growth and thyrotropic hormones, whereas, in Cushing's disease, a type of disorder associated with adenomas of the basophiles, there is another symptom complex involving chiefly adrenotropin. Nevertheless, the two types are not clearly divided because sexual failures, presumably caused by gonadotropin deficiencies are common in both.

The principle evidence refuting the argument for the master hormone of the pituitary has been the demonstration that the individual pituitary fractions could be obtained in chemically pure form. Nevertheless, such chemical data do not conclusively prove the point, because a large molecule with several prosthetic parts could conceivably be disintegrated and separated into several active fractions by chemical treatment. However, Dempsey and Searles (3) using environmental stimuli as a means of altering the rate of secretion of the various pituitary factors, showed that luteinizing hormone, adrenotropin and thyrotropin could vary independently, each

from the others. The discovery that thiouracil, by suppressing the inhibition normally exerted by thyrotropic hormone, causes a great increase in the production of thyrotropin, also allows observations on the physiological independence of hormones. Since in rodents the reproductive cycle, pregnancy, and lactation, continue normally after anti-thyroid treatment, it seems unlikely that the gonadotropic hormones or lactogen are seriously affected. Furthermore, the adrenal may be atrophic, normal, or hypertrophic in rats treated with thiouracil depending upon the concurrent stimuli to which the animals are exposed. These experiments suggest that the pituitary can secrete several qualitatively different factors at quantitatively independent rates.

Although considerably autonomy is possible for the individual hormones, the above considerations do not imply the absence of linked reactions or of multiple endocrine readjustments. In preceding sections it has been shown that environmental and nutritional stimuli such as light, cold, heat, and vitamin deficiencies can modify the activity of endocrine glands. As an example, after exposure to cold, the adrenal cortex enlarges and the thyroid becomes more active. These hyperactive glands are still subject to their normal regulatory mechanisms for injection of adrenocortical extract, or of thyroid hormone, reduces the responses of the respective glands. Similar reasoning applies to the effect of heat on the thyroid gland. In this case, the new setting of the endocrine mechanism is achieved at a point corresponding to lessened activity. It appears, therefore, that environmental stimuli set the regulatory mechanisms of one or several of the hormonal factors at new points corresponding individually to increased or decreased activity of the endocrine glands.

From the point of view of homeostasis these responses to exteroceptive stimuli represent changes in endocrine balance directed toward nullifying the external forces. Thus, thyroid and adrenal activity induced by cold results in an increased metabolic rate and increased utilization of carbohydrate. This augmented metabolism provides more heat and allows the animal's body temperature to be held constant despite the cold. These environmentally induced fluctuations in endocrine balance indicate that endocrine balance is not a static, specific endocrine interrelationship, but that it is a flexible, dynamic state changing and shifting constantly according to the particular constellation of stimuli operative at any instant.

For further understanding the homeostatic adjustments of the endocrine glands, there is great need for information about the concentration of the various hormones in the blood stream. It seems clear from the above that some environmental stimuli cause increased secretion and that other stimuli suppress the production of hormones. It is not clear, however, whether the increased or decreased rate of secretion corresponds to an elevated or

depressed concentration of hormones in the blood stream. Conceivably, an increased secretion would be necessary to hold a constant blood concentration if the hormone were fixed and inactivated by the end organ. It is also conceivable that the metabolic process regulated by the hormone might respond to an altered concentration without the hormone being used up in the process. In the latter type of system, the secretory rate might well be proportional to the blood concentration. New and sensitive analytical methods need to be developed to answer these questions about the nature of the homeostatic mechanisms.

A few examples may clarify the generalizations mentioned above. The rate of secretion of hormones can, for the most part, only be guessed at. In the case of the thyroid gland, however, Dempsey and Astwood (4) devised a procedure which permitted fairly accurate measurement of the rate of production of the rat's thyroid hormone. At normal room temperature, the rate of secretion corresponded to about five micrograms of thyroxin *per day. In cold temperatures, the rate doubled to approximately* 10 μg. per day, whereas in warm rooms the rate fell to about 1 μg. per day. Subsequently, estimates of the rate of secretion involving measurements with radioactive iodine have confirmed these figures. Now, a thyroidectomized rat given 1 μg. of thyroxine develops myxedema if kept at normal temperatures and this deficiency is so severe that death may occur in cold temperatures, yet this ration of hormone is sufficient for normal life at elevated environmental temperatures. A somewhat similar experience has been noted in humans transported from northern climates to the tropics. A slow but marked fall in basal metabolism occurs in adaptation to the warmer environment, yet the clinical symptoms of hypothyroidism do not supervene. Indeed, thyroid disease is less prevalent in the tropics than in northern latitudes, and even in the temperate zones the incidence of thyroid disease is greater in regions characterized by great changes in temperature than in the more equable regions.

Suggestive, but less accurately measured, data indicate that the adrenal cortex fluctuates widely in its hormone output depending upon the external or internal stress imposed upon the system. The adrenal cortex enlarges upon subjection of the individual to a wide variety of noxious stimuli. The types of stimuli which can cause adrenal hyperplasia are so varied that they are frequently grouped together under the name of "non-specific stresses". Cold, many drugs, surgical trauma, infection and many other agents or procedures all cause, as a common denominator, enlargement of the adrenal cortex and attendant signs of its hyperactivity. Moreover, if the stressful agent is prolonged in its action or severe in its nature, the adrenal will at first enlarge and subsequently undergo changes interpreted as indicating secretory exhaustion. The exhaustion stage is associated with

incipient collapse and death of the individual. On the other hand, less severe stress may cause prolonged hyperactivity of the gland without exhaustion. In such cases, pathological changes may occur in some of the organs which are the targets of the adrenal hormones, and a disease or diseases collectively called "diseases of adaptation" may ensue (Selye (5)).

Histochemical Investigations of the Endocrine Glands

The modern era of endocrinology has been brought about by a close union of the disciplines of morphology and physiology. One has only to recall the impetus given to endocrinology by the exposition of reproductive phenomena resulting from the work of Stockard and Papanicolaou (6), Allen (7) and Smith (8) to appreciate the value of using morphological end-points to study physiological processes. Following the classical papers cited above, myriad investigations were concerned with changes induced in the endocrine glands as a result of physiological experimentation. These experiments, however, were concerned for the most part with the simplest of morphological changes—atrophy or hypertrophy, detected merely as a change in size of the organ or tissue as determined by its weight or as examined in routine microscopical sections. Such investigations have led to our understanding of the trophic hormones of the anterior pituitary gland, to the stimulating effects of the sex steroids upon the male and female accessory organs and to the changes induced in the parathyroid by disturbed calcium metabolism and in the islets of Langerhans by altered blood glucose.

From the standpoint of gerontology, such observations have been of great value in delimiting the atrophic changes of the ovary and reproductive tracts during the menopause. A rather similar, but less sudden, involution of the testis also occurs in ageing males. In both sexes, both the gametogenic and the endocrine activities of the gonads decline or cease, leading therefore to sterility as well as to a kind of physiological ovariectomy or eunuchoidism.

In the other endocrine glands, an increasing incidence of involution or of pathological alteration accompanies age. However, it is by no means clear whether such incidental and sporadic changes should be considered part of the ageing process or as concomitant, but unrelated, pathology.

It seems evident from the above, that morphological changes have been of great value in detecting the physiological mechanisms of the endocrine glands. However, the phenomena so far examined have by no means exhausted the possibilities inherent in the morphological approach. For the most part, attention has been focused upon relatively gross changes in size and structure. Histological, rather than cytological methods, have been used. That cytological changes do occur upon endocrine stimulation

is well known (*vide* Moore's (9) assay procedure for androgens, involving increased cell height and secretory activity of the prostatic epithelium). Nevertheless, cytological procedures have been applied in endocrine experiments in only a casual, unsystematic fashion.

When one considers the histochemical and cytochemical procedures now available, the possibilities inherent in morphological investigation of the endocrine system become even greater. During the past decade, methods have been devised for the microscopical detection of many biochemical entities. Acidophilia and basophilia, long noted by histologists, may now be estimated with considerable accuracy (10). Polysaccharides, lipids, a variety of enzymes, and several inorganic substances may now be detected and localized with varying degrees of precision (11). In consequence, the histochemist or cytochemist now possesses an armamentarium of methods far superior to those available in the 1920's and 1930's when most of our current understanding of endocrine relationships was achieved. However, enough has been learned of the applicability of these newer methods to endocrine research to suggest strongly that significant advances will result from their more systematic use. In the following paragraphs, several examples will be given illustrating cytochemical observations which have been correlated with endocrine status.

The adrenal cortex secretes lipid-soluble hormones which are necessary for the maintenance of normal electrolyte, carbohydrate and protein metabolism. Since the adrenal cortex contains a remarkable amount of lipid material, the inference is clear that the morphologically detectable droplets must be related to the physiologically demonstrable hormones. Moreover, tests involving the solubility, fluorescence, birefringence and selective reactivity of these droplets have shown that their histochemical characteristics are remarkably similar to the chemical characteristics of the steroid hormones of the adrenal (Bennett (12), Dempsey (13)). The activity of the adrenal cortex can be modified greatly by experimental means (Selye (3)). After hypophysectomy, the activity of the gland is greatly decreased, whereas numerous situations involving physiological stress cause hypertrophy and increased activity of the gland. These considerations made it of interest to determine whether or not the altered activity of the adrenal cortex is reflected in an altered morphological appearance of the lipid droplets of the gland. An extensive series of investigations of this kind has been carried out by Greep and Deane (14) and collaborators. They have shown that the cytochemical reactions of the adrenal cortex reflect accurately the changed secretory activity of the gland, regardless of the experimental method utilized to alter the secretory activity. Moreover, they showed that disturbances in electrolyte balance cause an altered

appearance of the zona glomerulosa, whereas stress involving carbohydrate metabolism is associated with modifications in the zona fasciculata.

The cytochemical methods employed in the studies on the adrenal cortex can also be used to good advantage in the other organs of steroid secretion. Descriptions of the locations of reactive substances in the placenta have been published by Wislocki and Bennett (15) and Dempsey and Wislocki (16). The characteristically reacting lipids occur in the syncytial trophoblast of this organ. In the testis, Pollock (17) located carbonyl-lipids in the interstitial cells of Leydig, and Nelson and Heller (18) have presented a more recent and more thorough account. The ovary has been investigated by these methods, and descriptions of the changes occurring during the reproductive cycle have been published by Dempsey and Bassett (19), Everett (20), McKay and Robinson (21) and Barker (22).

In contrast to the situation in the adrenal cortex, emphasis in the investigations on the placenta and testis has been upon the localization of the carbonyl-lipids. The ovary, in addition, has been studied for changes during the reproductive cycle and pregnancy. Since in both the adrenal and ovary, the morphological procedures have proved adequate for detecting changed secretory status, the tools are available for an analysis of the effect of diet and other environmental variables upon the secretory activity of the reproductive glands and for investigations of the reactivity of these glands in juvenile, mature and aged individuals.

The reactions for lipids, which have proved most useful for studying the steroid-secreting organs, by no means exhaust the possibilities for cytochemical analysis. Following the publication by Gomori (23, 24) of a method for visualizing microscopically the phosphatase enzymes, a vast amount of work has been done utilizing these methods. Extensive surveys of the location of phosphatase in mammalian organisms have been published (Kabat and Furth (25)) and critiques of the specificity of the reaction have been essayed (Lison (26)). With respect to the endocrine system, Atkinson and Engle (27) have described a change in phosphatase activity of the uterine glands which is dependent upon the actions of estrogen and progesterone. In a somewhat more extensive endeavor, Dempsey, Greep and Deane (28) described the diminution or loss of phosphatase in a number of organs after hypophysectomy or gonadectomy, and its restoration after replacement therapy. It appears from these results that the activity of an enzyme can be used to estimate the degree of physiological activity of an organ.

Meyer and his collaborators have carried out an extensive series of studies on the activity of succinic dehydrogenase and other oxidative enzymes in the corpus luteum during the reproductive cycle (29). Their

results demonstrate marked changes in activity at different stages of the secretory cycle.

Mann and Mann (30, 31, 32) made the interesting discovery that large concentrations of fructose are to be found in the secretions of the male accessory glands. Moreover, the fructose content of the glands diminished and disappeared after castration, and returned again upon treatment with androgens. The fructose concentration could be used as an extremely sensitive androgen assay procedure, only small quantities of hormone being necessary to induce measurable increases over the level found in the castrated animal.

Among histochemical methods, the use of tracer compounds after labelling with radioactive elements has assumed more and more prominence in recent years. The tracer methods have become particularly important for studying the activity of the thyroid gland, since the thyroid hormone contains a large percentage of iodine, an element for which a suitable radioisotope is known. Iodides, either of the normal or isotopic variety, are rapidly withdrawn from the bloodstream into the thyroid gland, and incorporated into thyroxin which is stored in the thyroid colloid until secretory demand causes its release into the circulating blood. Experiments have been devised whereby the rate of uptake of radioiodide into the thyroid gland can be measured. Similarly, by other experimental devices, the rate of release of labelled thyroxin into the bloodstream can be determined. Such measurements provide indices of the rate of thyroid activity, and have been found useful in estimating the degree of hypo- or hyperfunction found in thyroid disease. Altered rates of activity have also been observed in animals subjected to cold and hot environments (33). So far, however, the normal fluctuations in rate of thyroid function from birth to old age have not been investigated by this means.

The foregoing account has attempted to select, from among many examples which might have been chosen, a few observations from the chemical morphology of the endocrine system which illustrate the possibilities for comparing structure and function. The available methods greatly increase the armamentarium of the histophysiologist. Procedures of a precision and sensitivity undreamed of a decade ago now exist. The application of these methods to a study of the ageing of endocrine organs should provide new information on the structural and functional changes which accompany age.

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AGEING OF HOMEOSTATIC MECHANISMS

NATHAN W. SHOCK

Baltimore

Other chapters of the present book have dealt in detail with age changes in specific organ systems. In some organ systems the changes with age are minimal, whereas in others they may be marked. In the higher organisms, at least, continuity of life is dependent not so much upon the functional activity of any one specific organ system as it is upon the integration of these systems and the effectiveness with which they can maintain stability of the cellular environment throughout the body. This general principle of physiology, first stated by Bernard (8) about the middle of the nineteenth century, was extended and expanded by Cannon (23 to 27), who first introduced the term "homeostasis" to designate the maintenance of this steady state in the cellular environment. The maintenance of uniformity of the internal environment may be regarded as the ultimate goal toward which all organ system activities are directed. With increasing complexity of organization within the animal, specialized functions are taken over by groups of cells in the development of the various organ systems; however, the various cells which contribute to the over-all maintenance of body equilibrium must also be maintained within certain limits of constancy with respect to acidity, temperature, oxygen tension, electrolyte composition, osmotic pressure, etc. Although cells in the same body may differ somewhat in the conditions needed for optimal performance, the general principle of homeostatic adjustment is applicable to all cells of the body.

The maintenance of homeostasis is effected by the interaction of numerous organ systems; thus, the regulation of the acid-base equilibrium is maintained by the interaction of chemical buffer systems in the blood and the excretory functions of the lungs and the kidneys. Furthermore, displacements in one chemical component of the blood may be produced by

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Baltimore

Other chapters of the present book have dealt in detail with age changes in specific organ systems. In some organ systems the changes with age are minimal, whereas in others they may be marked. In the higher organisms, at least, continuity of life is dependent not so much upon the functional activity of any one specific organ system as it is upon the integration of these systems and the effectiveness with which they can maintain stability of the cellular environment throughout the body. This general principle of physiology, first stated by Bernard (8) about the middle of the nineteenth century, was extended and expanded by Cannon (23 to 27), who first introduced the term "homeostasis" to designate the maintenance of this steady state in the cellular environment. The maintenance of uniformity of the internal environment may be regarded as the ultimate goal toward which all organ system activities are directed. With increasing complexity of organization within the animal, specialized functions are taken over by groups of cells in the development of the various organ systems; however, the various cells which contribute to the over-all maintenance of body equilibrium must also be maintained within certain limits of constancy with respect to acidity, temperature, oxygen tension, electrolyte composition, osmotic pressure, etc. Although cells in the same body may differ somewhat in the conditions needed for optimal performance, the general principle of homeostatic adjustment is applicable to all cells of the body.

The maintenance of homeostasis is effected by the interaction of numerous organ systems; thus, *the regulation of the acid-base equilibrium* is maintained by the interaction of chemical buffer systems in the blood and the excretory functions of the lungs and the kidneys. Furthermore, displacements in one chemical component of the blood may be produced by

the body in order to minimize changes in another. For instance, displacements may be produced in total electrolyte composition of the blood in order to readjust and maintain a given hydrogen ion concentration. This, for example, is what happens when the hydrogen ion concentration of the blood is displaced by the administration of excess acid and so-called "compensation" occurs (178). Under circumstances of increased hydrogen ion concentration, there may be temporary retention of bicarbonate ions with the resulting adjustment of pH to normal limits even though the bicarbonate concentration remains elevated.

It must also be recognized that the organism has available a number of different mechanisms for attaining the same end result. Thus, there are what might be called first and second lines of defense against displacement. These will be illustrated in more detail in the following sections. Existence of multiple methods of maintaining homeostatic equilibrium places certain limitations on experiments to evaluate homeostatic capacities. Comparison of measurements of displacement and recovery in a blood constituent or a physiological measurement induced by experimental stress may give identical results in old and young subjects. However, evaluation of the mechanisms involved may show that the older individual has had to call into play additional processes which were not required for the same adjustment on the part of the younger individual.

Cannon (22, 26) has emphasized the importance of the adrenal medulla and the autonomic nervous system in bringing about the internal adjustments upon which homeostasis depend. Much of his experimental work was directed toward demonstrating the importance of epinephrine and the sympathetic nervous system in emergency reactions; that is, to sudden changes in the external environment whether they be heat, cold, traumatic injury, such as burn or shock or mental states regarded as emotional. More recent research has indicated the importance of the adrenal cortex, the hypothalamus, and the anterior hypophysis as added elements in the coordinating mechanisms (81, 164, 168, 169). Thus, the hypothalamus as a center of the vegetative nervous system and the anterior hypophysis (or pituitary), as the chief coordinator of the endocrine glands, play important roles in the maintenance of homeostasis. The isolation of hormones for the anterior hypophysis which stimulate and activate the thyroid, adrenal cortex, and the gonads emphasizes the importance of this gland. The steroid hormones produced by the adrenal cortex participate in many regulatory functions; as for example, the regulation of electrolyte balance, blood sugar, etc. (164, 168).

Changes in the external environment or the activity of the organism which produce displacements in temperature, acidity, electrolyte composition, etc. must be counteracted by appropriate mechanisms within

the body to reestablish the optimal cellular conditions. Some of these environmental alterations may be in the nature of brief and immediate responses, whereas others may be of a long-term, chronic nature. All represent stresses to the organism. It is the purpose of this chapter to examine the effects of age on the integration of different organ systems in response to physiological stresses.

Temperature Regulation in Old Age

In mammals, body temperature is maintained within fairly narrow limits by a delicate balance between heat produced and heat lost (46, 47). Heat production is largely dependent upon the chemical changes occurring within the body. The tonic contraction of skeletal muscles, rhythmic contractions of the heart and the diaphragm, and the functioning of glandular organs all result in the liberation of heat. The rate of metabolic processes within the body, and the rate of basal heat production, is determined by the secretion of the thyroid gland. The level of activity of the thyroid is in turn influenced by the secretion of thyrotropic hormone from the anterior pituitary. Although the secretion of the thyroid is important in the regulation of heat production, metabolic processes go on within the cells even in the absence of thyroid hormone. For instance, in thyroidectomized animals, the output of heat is reduced by only approximately 40 per cent. In cold environments heat loss from the body is augmented and the internal temperature tends to fall. This calls forth a number of physiological mechanisms—some of which tend to minimize heat losses and others to increase heat production (148). For example, the surface blood vessels of the skin are contracted with the result that warm blood from the interior of the body is less exposed to cooling. Furthermore epinephrine is secreted by the adrenal medulla which accelerates the oxidation processes in the organism (10) resulting in increased heat production. If these mechanisms are insufficient to maintain body temperature, shivering, which like all muscular movement liberates heat, is automatically induced. Exposure to hot environments, which tend to raise body temperature, results in the opposite effects, that is, muscular tone is diminished and inactivity is the natural state resulting in a reduction of heat production. Heat dissipation is accelerated by (a) the outpouring of sweat which by evaporation cools the skin and (b) dilation of superficial vessels and the attendant exposure of warm blood to the body surfaces.

Resting body temperature

What then is the influence of age on the effectiveness of these adjustive mechanisms? In the first place it has been shown that under resting or

basal conditions, the internal temperature of elderly persons is maintained within the same limitations as that in young (5, 69, 116, 165). Howell (76) has recorded both mouth and axillary temperatures in 326 males aged 65–91. The averages were compared with similar measurements in 50 male and female nurses aged 20–30 years. The average values were slightly lower (0.02°F. for mouth and 0.64°F. for axilla) in the aged group than in the nurses. Since the latter group also included females, who show significantly lower temperatures than males, it cannot be concluded that an age difference exists. On the other hand skin temperature in older persons is slightly lower than in young subjects due chiefly to the diminished circulation in the skin of the aged (27, 91).

Response to cold

Although the older individual is able to maintain body temperature within normal limits under resting conditions, there is evidence that the response to high or low environmental temperatures is less effective in the old than in the young.

Munk (130) reported shivering in elderly subjects immersed in water at reduced temperatures that did not produce shivering in young subjects. More precise estimates of the response to cold have been reported by Krag and Kountz (98). Thirteen subjects aged 57–91 and 6 aged 22–36 were exposed to ambient temperatures of 5–15°C. for 45–120 minutes. Iron-constantan thermocouples recorded rectal temperatures and surface temperatures of the abdomen, midback, and mid points of the lower arm and leg. Serial determinations of oxygen consumption by the closed circuit method were also made. In general the young subjects showed little change in rectal temperature, whereas the aged subjects showed a fall of 0.5–1.0°C. during the exposure. The aged subjects showed a greater increase in oxygen consumption than did the young.

Response to heat

Clinical observations indicate that the aged individuals show impairment in their ability to adjust to increased environmental temperatures. It is known that heat prostration is more frequent among the aged than among the young. The death rate from heat stroke rises sharply after the age of [illegible]

shown that mortality rate in institutions for the aged increase during periods of prolonged high temperatures.

Experimental studies also indicate a slower rate of adaptation to heat

stress in the aged than in the young. Krag and Kountz (99) subjected 26 individuals, 14 aged 57–95 years and 12 aged 21–32 years, to ambient temperatures of 38–45°C. for 60–90 minutes. Measurements of rectal, oral, and skin temperatures as well as pulse rate, respiration rate, and oxygen consumption were made. Rectal temperatures were increased by 1.0–2.0°C. in both old and young subjects. However, the rate of change in rectal temperature was slower in the old than in the young.

The oxygen consumption was increased in all subjects but the response was more variable in the old than in the young. Furthermore, the increase in pulse rate was less in the old than in the young. Inability to dissipate excess heat quickly at high environmental temperatures is probably related to the sluggish circulatory responses reported in the aged (21, 43, 89, 132). In studies on the maximum rate of heat elimination from the hand, Pickering (141) found that under standard conditions the heat output in calories per minute per unit volume was approximately 33 per cent lower at age 70 than at age 25. In senile subjects the rate of water loss from the surface of the finger and toe tips was significantly lower in aged than in young subjects (20) thus reducing the potential heat loss from evaporation.

Basal heat production

Fundamentally, heat production is due to the chemical changes associated with the physiological processes going on in the organism. The common measure of these processes is the basal metabolic rate determined under standard conditions of rest and absence of digestive and absorptive activity. The classical observations by Magnus-Levy and Falk (114) indicated that the total basal heat production diminished with increasing age. It has become traditional to express heat production in terms of body surface computed from height and weight and it is commonly assumed on the basis of observations that the decrement in heat production observed in adolescence (172) and throughout middle life (11, 63) extends on into the higher age groups.

Relatively few subjects have been examined above the age of 70 years (177). Matson and Hitchcock (119) reported that the average basal metabolic rate of 14 men between the ages of 74 and 92 was 30 11 calories/sq. M./hr., a figure not greatly changed by including Benedict's (6) results from the study of 5 men between the ages of 74 and 87. A gradual drop in basal metabolism was observed by Kise and Ochi (90) in examinations of 94 Japanese subjects aged 50–93 years of age. However, only 4 subjects tested were above the age of 70. Kountz and his coworkers (95) have also reported diminished basal metabolism in elderly subjects. When the old subjects were divided into two categories on the basis of physical status

and activity, Kountz and Chieffi (94) found that the metabolic rate of the debilitated, weak, infirm subjects was higher at a given age than that of the more active and able group. On the contrary, Lewis (105) found no significant relationship between the apparent vigor of the aged individual and the basal metabolic rate. Individual differences between the 45 men, aged 65–101, were very large. In fact, many of the subjects above the age of 80 years had metabolic rates as high or higher than the average of the 40-year group. Despite the increased range of individual differences in the aged, statistical analysis of the observations showed a linear decrease for the average curve between the ages of 40 and 90 years. The average value for basal heat production diminished from 36.4 cal./sq. M./hr. for the 40–49 year old subjects to 33.6 cal./sq. M./hr. for the 80–89 year group—a total decrease of less than 10 per cent.

Shock and Yiengst (181) determined basal metabolism in 130 males between the ages of 50 and 92. In this series the average basal heat production per unit of surface area per hour fell from 35.9 to 31.3 cal. over this age range. When these observations are compared with data obtained by the same experimental procedures in adolescent children and young adults, it appears that the age change is relatively slight beyond the age of 50 years.

One of the most troublesome problems in considering basal metabolism is that of making appropriate corrections for body size. Obviously the fundamental data which are desired are an expression of the production or oxygen consumption per unit of active protoplasm in the animal. Surface area has been chosen largely as a matter of expediency and because it minimizes individual variations (173). There is, however, good evidence that surface area is only remotely related to active protoplasm and that some more fundamental physiological measurement should be used. A number have been proposed, such as fat-free body weight, extracellular fluid (35), and total body water, but no extensive data on age changes in these measurements are available.

Only a few studies on the effect of age on the oxygen consumption of isolated tissue have been made. A decline in the respiratory oxidation of articular cartilage has been reported by Rosenthal, Bowie, and Wagoner (156, 157, 158). They attributed this decline to a gradual failure of the oxygen activating component of the respiratory enzyme systems. Lazovskaya (101, 102) has reported a decrease in the oxygen uptake in the blood vessels of the old rats when compared with young animals which he believes is due to a reduction in the activity of the succino-dehydrogenase and cytochrome oxidase enzyme systems. A similar reduction in the oxidation processes in muscle tissue of old birds (56) and guinea pigs (32) has been reported.

When homogenates are used, some tissues have shown a significant decrease in metabolic activity with age, while others have not. Reiner (149) observed a marked decrease in oxygen consumption of brain tissue homogenates prepared from aged rats, whereas no significant changes were found in liver homogenates. He concludes that enzymatic changes accompany the ageing process and that these changes cannot be attributed to alterations in permeability of the cell surface or other structural factors. In contrast to Reiner's results, Pearce (139) has reported a significant reduction in oxygen consumption with increasing age of not only liver but kidney and cardiac tissue also. According to his results, age changes were greatest for liver tissue; intermediate for cardiac tissue; and least for kidney.

Victor and Potter (191) found a decrease in oxygen consumption in lymphoid tissue of old mice. They believe that old mice have a higher aerobic and anaerobic glycolytic rate than do young mice. Thus definitive data which will answer the question of whether the metabolic rate per unit of active protoplasmic tissue is significantly diminished in old age have not yet appeared. Nevertheless, it is apparent that the total heat production for the entire organism does diminish with age.

Thyroid function

A number of reasons for the reduced heat production in elderly subjects may be suggested. First of all, there is ample evidence of structural involution of the thyroid gland itself (1, 44). Dogliotti and Nizzi Nutti (44) found that in the aged the number of follicles is reduced, and in those remaining the colloid is reduced and the epithelium is hypertrophied. Andrew and Andrew (1) have also reported clusters of very small follicles lined with cuboidal epithelium in the thyroid glands of older animals. While these histological observations are of interest, their interpretation in terms of physiological function is difficult since the inference of functional activity from structural changes is not without hazard. We simply do not know how far reduction in size of the gland, reduction in size and number of epithelium cells, reduction in vascularity, and increase in connective tissue can go before the output of the thyroid hormone falls below that required to maintain optimal metabolic rates. With the development of more precise techniques for estimating thyroid function such as the rate of uptake of radioactive iodine, these questions are open to experimental attack.

Since the level of functional activity of the thyroid is regulated by thyrotropic hormone produced by the pituitary, the reduction in metabolic rate of older people might be due to diminished pituitary function. In fact, Findlay (52) has postulated pituitary insufficiency as a primary factor in ageing. While attractive, this hypothesis breaks down under critical

evaluation since some of the hormones produced by the putuitary are excreted in increased quantities in older people; as for example, the gonadotropic hormones in women beyond the age of menopause (64, 88, 137). Unfortunately, we do not have available quantitative tests which are adequate for evaluation of individual differences in pituitary function in normal subjects.

It is also possible that with increasing age the responsiveness of individual tissues to thyroid hormone diminishes. As indicated previously, our knowledge of changes in metabolism of individual tissues with age is most scanty. Although a number of studies have reported a diminution in oxygen consumption with increasing age, none of them have given any information about the responsiveness of the enzyme systems studied to thyroid hormone.

Muscle strength

Finally, the diminished heat output in older people may be attributed in part to lessened muscular vigor and activity. Reduced activity and muscular atrophy are common clinical observations in older people.

Quantitative measurements of the strength of various muscle groups show a maximum at ages 25 to 30 years followed by a gradual decrement. In 1835 Quetelet (147) found that the strength of hand grip of 60-year old males had declined by approximately 40 per cent of that observed in subjects aged 25–35. Galton, 1884, collected similar observations on approximately 7,000 subjects attending a health exposition. These data, analyzed by Ruger and Stoessiger (159), showed a decline of only 10 per cent between the ages of 30 and 60, although at age 80 the average strength of grip had declined by 35 per cent of the 30-year old group. In 1921 Rejs (150) investigated muscle strength in 3,000 Dutch men and women. The maximum strength was maintained between the ages of 25 and 37 years. At the age of 40–45 years it was still 96 per cent of the maximum and at the age of 50 years it had declined only to 92 per cent of the maximum. Simonson (183) interprets the differences between Quetelet's and Rejs' results as evidence that the increased life duration taking place between 1835 and 1921 was accompanied by better maintenance of muscle strength and possibly also of other functions important for over-all working capacity. Similar measurements on industrial workers up to the age of 65 showed a 30 per cent drop between the ages of 30 and 65 (190). As pointed out by Fisher and Birren (53), the data available cannot be taken as an indication of the exact relationship between age and strength since grave sampling errors may interfere with comparisons of the old and young subjects. For example the use of industrial populations will eliminate the less capa-

ble among the older age groups. Consequently, these observations in all probability overestimate the mean strength of the elderly.

Heat loss through the skin

The primary mechanisms of heat loss are through changes in the blood supply to the skin, sweating, and evaporation of water from the respiratory passages. The structural changes in the skin in old age are presented in detail in Chapter 29. The atrophy attended by dryness, roughness, and loss of elasticity contributes to the impairment of heat transfer. Of even greater importance is the partial disappearance of capillaries. Furthermore, the condition of the remaining blood vessels and their ability to dilate under conditions which produce vasodilatation is apparently reduced All of these factors working together interfere with a ready discharge of heat from the body.

Summary

The foregoing considerations reveal gradually restricted powers of adjustment to both high and low external temperatures as old age progresses. The body temperature with moderate conditions is maintained within the usual range of diurnal variation. However, the limits of adaptation tend to become gradually narrower as one passes through the seventh decade to the later years of life.

Regulation of Blood Sugar in Old Age

Regulation of the blood sugar level is achieved by storage in times of plenty, by release in times of need, and by overflow through the kidneys in times of excess. The storage of sugar is chiefly under the control of the parasympathetic mechanisms. The release of sugar to counteract falling blood levels may be effected by a number of mechanisms (67), such as the sympathetic-epinephrine system, the thyroid and posterior pituitary, as well as the anterior pituitary and adrenal cortex (187).

Resting blood sugar levels

In view of the numerous mechanisms by which blood sugar levels may be maintained, it is not surprising to find that normal levels are ordinarily observed in older individuals under standard basal conditions. While some investigators have reported slightly elevated values in older people (83, 140, 144, 155) the differences are not marked, and other investigators have found no systematic differences (115, 121, 146). Furthermore, most of these studies have been carried out on hospital patients and few values are available on normal older people. The inclusion of early, mild diabetics

within the sample would tend to increase the mean values. Until observations coupled with careful clinical evaluations are available, the small differences in blood sugar values at higher ages may be regarded as insignificant.

Oral glucose tolerance tests

The efficacy of the mechanisms for absorption, storage, and utilization in blood sugar can be assessed by observing the speed with which the organism reestablishes normal blood levels following experimental displacements. The oral glucose tolerance test is performed by giving the subjects 80–100 gm. of dextrose in 250 cc. of water by mouth. Blood samples are drawn at 30, 60, 90, 120, and 150 minutes. In young subjects, blood sugar temporarily rises sharply from levels of 80 to 100 mgm. per 100 cc. during the first half-hour to reach 130 to 170 mgm. per 100 cc. and gradually returns to normal levels within 2 to 2½ hours. In older subjects, the rise is usually greater and the return to normal levels requires more than 3 hours (42, 71, 73, 84, 92, 107, 115, 155, 170, 188). However, other varieties of curves are also found, as for instance, flat curves where the rise is smaller than that obtained in younger subjects and persists over a period of more than 3 hours (73). In patients suffering from diabetes, the initial rise is much higher (greater than 180 mgm. per cent) and remains elevated for more than 3 hours (128). Porter and Langley (144) made tests on 50 normal subjects; ten in each decade from 30 to 80 years. With increasing age up to 70, the initial rise was greater and more time was required for recovery. *On the contrary, subjects between the ages of 70* and 80 years showed smaller rises but prolonged duration of increased sugar level.

In a study of 28 healthy old men, the glucose tolerance test gave normal curves in only four cases (115) Among the abnormal curves, eleven manifested a storage deficit, that is, a lengthening of the curve so that it did not return to the fasting level in two hours. There were 7 cases of "lag curves" where the blood sugar rises slowly but exceeds the kidney threshold and 2 cases of flat curves probably resulting from slow absorption. Four of the subjects responded to the test with a typical diabetic curve.

Rømcke (155) reported results on 10 cases between 61 and 70 and found that the maximum rise was greater in the older than in the younger age groups. Similar results were reported by John (84) on the basis of 1,727 tests on subjects of different ages. The incidence of the diabetic type of curve rose from about 10 per cent in the cases of the fourth decade to about 50 per cent in the seventh. On the other hand Nitzulescu, Ornstein, and Sibi (133), who examined 40 subjects between the ages of 50 and 85 years of age did not find any variation of the glycemic curves correspond-

ing to the advancement of age. Horvath, Wisotsky, and Corwin (73) performed repeat oral tests on 12 patients between the ages of 60 and 70 years of age. They reported an increase frequency of impaired storage curves, flat curves, and diabetic curves among their subjects. However, there was a poor correlation between the type of curve observed in the same patient on successive tests. In one patient 67 years old, they made 11 consecutive tests 18 days apart and obtained normal, deficient storage, flat, and frank diabetic curves on successive tests in the same subject. Similar fluctuations in the type of tolerance curve obtained on the same subject on different days have been observed by Hofstetter, Sonnenberg, and Kountz (71).

These results tend to illustrate the unreliability of single oral tests. Some of this unreliability may be related to differences in rate of absorption. Furthermore, the delay in the rise in blood sugar observed in many of the tests of older people may also be related to absorption differences and hence cannot be interpreted in terms of carbohydrate metabolism alone.

Intravenous glucose tolerance tests

The intravenous administration of the glucose test load eliminates the absorption variable. Smith and Shock (185) have reported the results of intravenous glucose tolerance tests on older patients. Figure 1 compares the average curve for 20-year olds with that observed in a group of 20 80-year olds. Analysis of these data indicate that the rate of removal of intravenously administered glucose is slower in the older subjects than in the young. This results in an increased incidence of delayed curves among the older subjects and is evidence of impaired storage mechanisms and/or excretion in older subjects. In an attempt to elucidate the mechanism of the delay further, Smith (184) compared the changes in blood pyruvate level following the administration of glucose in the aged with similar tests in diabetics. In the diabetic subjects, there was a rise in blood pyruvate levels, whereas the older subjects (with delayed glucose response curves) showed flat pyruvate curves similar to those observed in normal adults. This finding is taken as presumptive evidence that the delayed response in the older subject cannot be attributed to a deficiency in insulin production alone.

With increasing blood sugar levels, the reabsorptive mechanism for glucose in the renal tubule may become saturated with an attendant loss with sugar in the urine. The plasma level at which this loss occurs is a function of the capacity of the renal tubule to reabsorb glucose as well as the rate of formation of glomerular filtrate in the kidney. Consequently, the older concept of "renal threshold" loses much of its significance. According to Marshall (115), the renal threshold rises from 170 to 180 mgm.

per cent in young adults to 200 to 210 mgm. per cent in the healthy aged. More precise estimated of the reabsorptive capacity of the renal tubules for glucose indicate that whereas young individuals (mean age—35 years) are capable of reabsorbing 328 mgm. of glucose per minute, this maximum capacity falls with age to approximately 224 mgm. per minute in the 80-year olds (124). *Since the glomerular filtration rate diminishes with age* (37) (the ratio Cl_f/Tm does not change with age), the requirements for

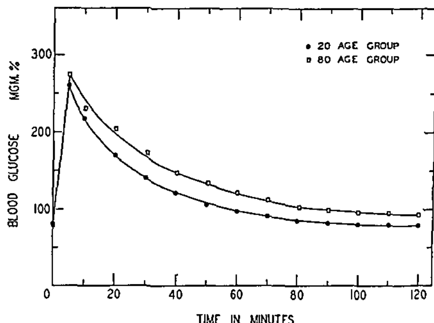


FIG 1. Average intravenous tolerance curves. ●——●, 20–29 year age group; □——□, 80–89 year age group. From Smith and Shock (185).

glucose reabsorption are proportionately reduced in the old subjects so that no urinary loss of glucose occurs under normal circumstances.

Response to hypoglycemia

The effects of age on responses to hypoglycemia have not been systematically studied. In young adults the injection of small amounts of insulin results in a rapid fall in blood sugar followed by recovery. Himsworth and Kerr (66) reported numerous subjects in the later years of life who failed to show this response to the injection of insulin. These authors attribute their results to the excessive secretion of the anterior pituitary gland, extracts of which induced refractiveness to insulin in normal animals.

Summary

Although much experimental work remains to be done to elucidate the mechanisms involved, the fact that advancing age imposes limitations on the regulatory mechanisms for maintaining blood sugar levels is apparent.

Regulations of the Acid-Base Balance in Old Age

The acid-base equilibrium of the blood and tissues is determined primarily by the ratio of the concentration of bicarbonate to that of carbonic acid. Under normal circumstances, this ratio is approximately 20 to 1 resulting in a pH of about 7.40. Under conditions of increased metabolic activity, the liberation of acid metabolites tends to disturb this ratio. This is particularly true when the increased activity takes place under conditions of reduced oxygen tension; as for example, reduced oxygen of the inspired air or in lowered oxygen tension in the tissues due to inadequacy of the transport system.

Regulation of the acid-base equilibrium is effected primarily by two mechanisms. The first is through elimination of carbonic acid by the lungs or increased retention by reduced ventilation. These processes represent effective devices for rapid adjustment by alterations of the carbonic acid content of the blood. When fixed acids are released into the blood, carbonic acid is displaced from the large pool of bicarbonate present and consequently tends to lower the bicarbonate concentration The increased carbonic acid is readily eliminated under normal circumstances through the lungs, restoring the system to equilibrium. On the other hand, conditions leading to accumulation of bicarbonate may be compensated temporarily by reduced ventilation and consequent piling up of CO_2. Thus, the ratio of bicarbonate to carbonic acid concentrations is maintained, resulting in a normal pH.

The second mechanism of importance in regulating acid base equilibrium is the kidneys. It is through the kidneys that increased quantities of acid or base are eliminated. Adjustment by this mechanism requires considerably more time than adjustment of the carbonic acid mechanism. Both processes are, of course, dependent upon adequacy of the blood supply to the kidneys and the lungs.

Pulmonary factors

Adequate pulmonary regulation of the carbonic acid content of the blood is dependent upon the movement of air in and out of the lungs, the rate of diffusion of carbon dioxide across the alveolar membrane and the adequacy of the blood supply to the lungs. It has long been known that advancing age is associated with the reduction in the vital capacity, that

is, the greatest amount of air which can be forced voluntarily from the lungs after the deepest intake.

Although the earliest studies of vital capacity were reported by Hutchinson (80), the most detailed statistical analysis of age changes was reported by Holzinger (72) on the data collected by Galton. The average vital capacity attains a maximum value (3,750 cc. in males; 2,500 cc. in females) between the ages of 20 and 30 years. After the age of 30–35, the vital capacity gradually falls to values of approximately 1,800 cc. for 85-year old males in the Galton data. Later investigators, studying larger numbers of subjects at the higher ages, report significantly higher values at ages 70–90. Levy (104) examined 110 men 60–94 years of age and 71 women age 60–92. The average vital capacity of the males fell from 2,980 cc. at age 60–65 to 2,350 at ages 86–90. Corresponding values for females were 1,985 cc. at age 60–65 and 1,460 cc. at age 86–90. Miller (123) has reported essentially similar values in 744 men aged 40–94. Although there is a significant drop in vital capacity with age, there are large individual differences so that the correlation between age (20–70 years) and vital capacity is only about −0.4 (3, 193).

The diminution in vital capacity in old age may be due in part to loss of elasticity of the lungs, but is also influenced by weakening of the intercostal muscles and a stiffening of the attachments of the ribs. Saxton, Barnes, and Sperling (163) have shown that the distensibility of the lungs is markedly diminished in old rats. Christie (34) has also demonstrated a marked reduction in elasticity of the lungs in emphysema. According to Burger and Schlomka (19), the water content of the costal cartilage diminishes with age and the calcium content increases. They found that whereas the calcium content of the cartilage was only 125 mgm. per 100 gm. dry substance in the second decade of life, it was 617 in the fifth and 1,399 in the seventh decade.

It should, however, be pointed out that the vital capacity is in itself of minor significance in the elimination of carbonic acid. Of greater importance is the determination of the residual air, or the amount of air that remains in the lungs after expiration, and the adequacy of alveolar ventilation. Using a dilution technique, values for total lung volume, complemental air, reserve air, and residual air have been determined in 58 males and 31 females aged 10–70 years by Whitfield, Waterhouse, and Arnott (193). Although negative correlations with age were found for all the respiratory variables, the correlations were all low (less than 0.50). Thus systematic observations of the dead space or the proportion of the total lung volume which does not enter into active gas transfer have not been made in subjects over the age of 70.

Another factor of considerable importance in the transfer of gases is

the rate of flow of air in and out of the respiratory passages. The air velocity is related to the elastic qualities of the lungs as well as the motion of the chest and diaphragm. Although techniques are available to estimate air velocities (55, 145), no systematic studies of older people have been reported.

The maximum breathing capacity, determined by short periods (20 sec.) of voluntarily ventilating the lungs at the maximum rate and volume, has been determined in very few subjects over the age of 65. Among young adults (age 18–30), there is no significant correlation with age (58). No doubt there is a significant decrement at higher ages, but no adequate data are available. Another factor of great importance in the regulation of the carbonic acid content of the blood is, of course, the rate of transfer of CO_2 across the alveolar membranes. The accumulation of fluid in the pulmonary alveoli may tend to reduce the rate of elimination of carbonic acid from the blood. Retention of carbonic acid is one of the principal effects of emphysema (36, 166).

Pace and his coworkers (138) have reported preliminary results on the ability to eliminate carbon monoxide from the lungs in 14 subjects between the ages of 20 and 65. The rate of elimination diminished with increasing age ($r = 0.82$). These results indicated a significant drop in transfer rates for CO even between the ages of 20 and 40 years. Since the adequacy of the pulmonary circulation is also involved in the studies which measure the rate of absorption or elimination of gas, the results cannot be interpreted as clear-cut evidence of changes in pulmonary permeability. Thus, Jones (85) has used similar data on the rate of elimination of nitrogen from the lungs when breathing pure oxygen to calculate the average rate of blood perfusion of the modal tissue serving at the source of nitrogen. According to these calculations, the average blood perfusion is reduced by over 50 per cent between the ages of 20 and 35 years (86).

Renal factors

Long-term adjustments of the acid-base equilibrium are effected through the kidney which excretes the excess acid or alkali. As shown in other chapters, ageing places certain limitations on the functional capacity of the kidney. With increasing age, there is a loss of structural elements. In addition the blood flow to the kidney is reduced, the rate of glomerular filtrate is impaired, and the maximum rate of excretion of substances, such as diodrast and PAH is reduced (37, 176). Consequently, one might expect impairment in the ability to regulate the acid-base equilibrium.

With increasing age there is a statistically significant reduction in the pH of the serum in resting conditions, that is, the blood becomes progressively more acidic (180). However, the average change is from pH of 7.40

at 25 years to 7.36 at age 90—a change that is still within the limits of normality for young adults by the usual clinical standards. The reduction in pH is associated with a small rise in CO_2 tension and a slight drop in serum bicarbonate levels, neither of which are statistically significant.

Although the glomerular filtration rate, effective renal plasma flow, and Tm diodrast were reduced by 35 to 45 per cent, the basal acid-base equilibrium of the blood was maintained within normal limits in the same subjects.

Although the acid-base balance of the blood can apparently be maintained within normal limits by older persons under basal conditions, the application of an extra physiological load on this mechanism brings to light certain limitations in the aged. The administration of acidifying or alkalizing substances produces a temporary shift in the acid-base equilibrium of the blood. In young adults the recovery is effected within a period from 8 to 10 hours (178). In aged subjects, however, the rate of recovery is much slower following the oral administration equivalent amounts of these substances (179). It has also been shown that young adult dogs recovered from the reduction in alkaline reserve following the administration of morphine sulphate more quickly than did old animals even though no histological evidence of kidney damage could be found in the old animals (113).

Exercise as Physiological Stress

Adequate adjustments to the physiological stress of exercise may involve practically every organ system in the body. Although functional limitations in the performance of the heart, blood vessels, kidney, endocrine system, or respiratory system are undoubtedly of importance, the over-all response to exercise is dependent upon the appropriate integration and coordination of the responses of many organs. The primary goal toward which all adjustments are directed is increasing the supply of oxygen to the functioning tissues. Thus the extra demand for oxygen may range from the ten-fold increase often observed after exhausting muscular work (152, 173, 175) to the almost undetectable increase in oxygen demand following activities of the higher nervous centers (33). Increased delivery of oxygen is effected by increases in blood flow and a more complete removal of oxygen from arterial blood in its passage through tissues. Delivery of oxygen to functioning tissues is aid by dilation of the capillary bed followed by an increase in pulse rate, blood pressure, cardiac output, and circulation rate. Under conditions of heavy work, these mechanisms are inadequate to maintain the supply of oxygen and the oxygen tension in the tissues falls, resulting in increased acid formation.

There is also an increase in the carbon dioxide production with a consequent shift in the acid-base equilibrium of the blood toward the acid side (174). Adjustment to this displacement is effected by increased elimination of carbon dioxide through the lungs as evidenced by augmented respiration rate and volume. Fixed acids, such as lactic, may be excreted in part through the kidneys and in part oxidized further to carbon dioxide and eliminated by way of the lungs during the recovery period. The increase in respiratory volume gives more effective mixing of gases in the lungs with an increased opportunity for the transfer of oxygen into the blood, as well as the elimination of carbon dioxide.

The increase in heat production resulting from muscular activity is dissipated by vasodilation of the vessels in the skin and by augmented sweating. Endocrine factors also play a part in the adjustment to exercise. The release of epinephrine from the adrenal medulla increases the glucose available to the contracting muscle by its release from the glycogen stores of the liver. There may also be a contraction of the spleen with a release of additional red blood cells into the blood stream to augment the capacity for transport of oxygen from lungs to tissues With prolonged exercise, the liberation of steroid hormones from the adrenal cortex is evidenced by increased elimination of 17-ketosteroids.

Exercise performance and work capacity

These processes attain their maximum effectiveness and coordination in young adults (175). The effects of narrowing limits of adaptation of the respiratory and circulatory systems with increasing age may be found in the results of competitive sports (153). Sprinting records are commonly held by young men in their teens and their twenties. The hundred-yard dash was first run in 9.4 seconds by Wykoff when he was 21. Performances calling for bursts of speed and performance under anaerobic conditions are best met in younger men. On the other hand, where judgment and endurance are of importance, records are held by older men (103). For instance, the ten-mile record was made by Nurmi at the age of 31 and by DeMarr who ran Marathon races many times between his 22nd and 49th year. Although there is a reduction in the ability to perform fatiguing, muscular work with advancing age (4, 183), there are wide individual differences in the effect of age on power and endurance Observations on a single subject from the fifth to eighth decade indicate that while the working capacity decreased steadily at 71 years, being 50 per cent of what it had been at 41 years, efficiency was much the same at each age (39). Although this subject was not exceptionally endowed physically, he had participated in hiking and mountain climbing since boyhood. In this subject the maximum

work output on the bicycle ergometer was observed at the age of 41 years (1,830 kg. m. per minute). At the age of 57 the maximum rate was 60 per cent of this and at 71, only 50 per cent (40).

Oxygen transport

One of the factors limiting physical performance in older subjects is the diminished ability to transport oxygen. Robinson (152) showed that the increase in oxygen uptake during work proceeds at a slower rate in old than in young men. He also found that the maximum amount of oxygen transported from the lungs fell from 53 cc./kg. body wt./min. at age 17 to 26 cc./kg. body wt./min. at age 75. More recently Wright (195) determined the quantity of oxygen removed per minute from respired air during the 5th and 6th minute of the most intense exertion tolerable for 6 minutes on the treadmill in 41 males aged 25–45. Over even this restricted range, a correlation of −0.614 (S.E. = 0.097) was found between this function and age. Norris, Yiengst, and Shock (135) have shown that subjects above the age of 80 require more oxygen per kg. m. of work performance than do younger subjects.

Other evidence that older subjects are less able to transport adequate oxygen supplies to tissues than are younger ones is offered in the greater formation of fixed acids in older subjects after exercise. For instance, Mori (127) subjected men age 17 to 57 years to standard exercise for 10 minutes on a bicycle ergometer. He found that in 4 youths of the second decade, there was a reduction in the alkaline reserve of the body by about 4 volumes per cent. In 13 subjects in the fifth decade, the reduction was approximately 12 volumes per cent. Unfortunately, the presence of lactic acid was not investigated, but it is reasonable to assume that the decreased alkaline reserve was due chiefly to an accumulation of lactic acid. Robinson (152) observed that when subjects of different ages are made to perform the same work (walking on a treadmill at the rate of 3.5 miles per hour at a grade of 8.6 per cent increasing metabolism about seven fold over basal values), the extra amount of lactic acid demonstrable in the blood was more than twice as much at the age of 63 than at the age of 24½ years.

The rate of recovery of oxygen consumption and CO_2 elimination following exercise also diminish with age. A significant lowering in the recovery rate of oxygen consumption was found between the ages of 18 and 35 (175). In observations on 32 subjects (age 18–68 years), Berg (7) found a correlation of 0.71 between the rate of recovery of O_2 consumption after exercise and age. The corresponding value for CO_2 elimination was 0.93.

Older subjects also show a greater increase in respiratory volume following strenuous exercise than do young. Furthermore aged subjects re-

quire a greater augmentation in order to obtain a given level of oxygen utilization than do young subjects (135).

Vascular changes

Vascular changes also contribute to age differences in the response to exercise. In an examination of a variety of muscles, Buccianti and Luria (17) found that in old persons there is a laying down of interstitial colloid and a thickening of a sheath of elastic tissue which envelops the individual muscle fiber. The capillaries lie in this interfibrillar region. Even if they should dilate in the usual manner when the muscle becomes active, the diffusion of the respiratory gases, expecially oxygen which has a low diffusion coefficient compared with carbon dioxide, might meet obstruction because of interposed extravascular material.

Blood pressure

Many studies on the relation between age and blood pressure have been made. There is common agreement that average values of both systolic and diastolic pressures rise with advancing age, although investigators differ as to the age at which the increment begins and its extent (13, 38, 57, 74, 82, 87, 106, 118, 120, 122, 151, 154, 160, 161, 162, 189, 192). Most of the observations show a gradual rise in systolic pressure beginning as early as 20 years. Master et al. (118) show a rise from 122 mm. Hg at age 20 to 142 mm. Hg at age 65 in males. In females, the corresponding values are from 116 mm. at age 20 to 142 at age 65. The diastolic pressure also rises from 76 to 86 mm. Hg in males and from 72 to 85 mm. Hg in females Above the age of 65, the most extensive observations are those of Wetherby, (192), Russek and Zohman (161), and Howell (74, 76). All observations agree in showing a further rise in the average values beyond the age of 65. Russek and Zohman (161) give average values of 164/90 mm. Hg in 126 males aged 85–95 years. With increasing age, there is also a marked increase in the range of individual differences (σd) in blood pressures (192). Robinson and Brucer (154), as well as Bruck (16) contend that when all subjects with detectable pathological changes are excluded, the resting blood pressure does not change appreciably with age (118 to 120 mm. Hg between the ages of 20 and 75 years). This assertion raises the philosophical distinction between "average" and "normal" values. There is no question but what the average values of blood pressure increase with age. Whether these are to be regarded as normal or not is a philosophical question on which each investigator must reach his own decision.

Under conditions of maximum physical work, the blood pressure rise does not change significantly with age (152). However, it has been shown

that under conditions of standardized exercise which does not represent all-out exertion for younger subjects, the increment in blood pressure is significantly greater for old than for young (134). Thus, there is evidence that for a given level of exercise the cardiovascular disturbance is greater in old than in young. The elasticity of the arterial walls is diminished as shown by direct measurements on excised strips of arteries (97, 131, 194), as well as by measurements of pulse wave velocity (14, 60, 70). For example, Hallock (60) made observations on nearly 400 persons between the ages of 5 and 65 years. The minimum pulse wave velocity was observed at the age of 14 years (5.2 m. per sec.) and increased on the average to 8.5 m. per sec. at 84 years. These results indicate a gradual loss of elasticity with increasing age. On the basis of data now available, it is impossible to separate the possible respiratory and cardiovascular factors that may contribute to the observed age differences.

Heart rate

Although average values for resting heart rate tend to diminish with increasing age (75, 76), the increased incidence of irregularities in rates in the aged offer evidence of impairment in the regulatory mechanisms (100). According to Howell (76), the resting heart rate falls from a mean of 76 beats per minute at age 60–64 to 69 beats per minute at age 80–84, but increases again to 73 at age 85–89 and to 79 at age 90–94. Robinson (152) has shown that one of the characteristics of older subjects is their inability to increase their heart rate after severe exercise to as great an extent as younger people. The mean of the maximum heart rates (after exercise) of a group of nine boys having an average age of 14.2 years was 196 beats per minute; whereas, in a group of six men with an average age of 63, the mean maximum rate was 163—a reduction of about 17 per cent. On the other hand, when nonexhaustive exercise is performed in standard amounts, the increment in heart rate is greater in old subjects than in young (117, 134). Further evidence of impaired control of heart may be found in the results of postural changes in young and old subjects. Norris, Shock, and Yiengst (134), as well as Graybiel and McFarland (59) have shown that when subjects are passively tilted from supine to the upright position, the normal response of an increment in pulse rate is less in old subjects than in young. These results have been attributed to diminished sensitivity of the carotid sinus mechanism to changes in hydrostatic pressure.

Summary

Evidence is available to indicate that not only do individual organ systems show impairment, but also that coordination is impaired in old people.

Response to Generalized Stress and Resistance to Injury and Disease

The role of the pituitary and adrenal gland in adjustments to generalized stress situations has been emphasized by Selye (169). The increase in death rates that take place with advancing age is evidence of a diminished capacity to adjust to physiological stress (182). However, attempts to isolate the specific factors responsible for diminution in ability to adjust to generalized stresses have not been very successful.

Adrenal-pituitary reaction to stress

A number of investigators have shown that the increased excretion of urinary steroids is one index of the responsiveness of the adrenal-pituitary system. Although the excretion of 17-ketosteroids under resting conditions diminishes progressively with age (61, 62, 96), we do not know whether the increment, as an expression of the response to stress, is greater in old than in young subjects. When a specific physiological stimulus to the adrenal gland is administered (ACTH), there is a greater excretion of 17-ketosteroids and uric acid in young subjects than in old (142, 143, 186). However, in view of the diminished excretory ability of the kidney in older people, it cannot be assumed that this index is simply a reflection of activity of the adrenal cortex.

When other indices of adrenal cortical activity are examined, as for example, the reduction in eosinophil count, no age differences in response to a single injection of ACTH were observed (186). On the other hand, stimulation of the pituitary gland to release endogenous ACTH, as for example, the injection of a single dose of epinephrine showed a significantly lower response in old subjects than in young (186). While these observations cannot be interpreted as proof of diminished pituitary reactivity, they offer presumptive evidence.

General adaptation syndrome

Selye (168) has divided the responses to stress situations into three major components. The first phase, or the alarm reaction, is characterized by widespread, generalized physiological responses. The second phase is termed the stage of resistance during which time the adaptive mechanisms have been brought into play and the responses to the stress are minimized. The third phase, the stage of exhaustion, is characterized by a breakdown of the adaptive mechanisms and impaired resistance to stress. This concept of the general adaptation syndrome has been applied to the problem of ageing and the so-called degenerative diseases. Thus, many of the diffuse collagen diseases may be likened to a process of accelerated ageing similar to the

normal ageing which occurs under the influence of the stresses and strains of *daily life*.

Evidence may be found to support the concept that the very young organism is still unadapted to the stress situations of life and hence reacts violently to them, but rapidly acquires and maintains adaptation to almost any change. Conversely, the adult has already acquired adaptation to most of the stimuli he encounters and has become resistant to them; however, the senile animal has gradually lost the power of learning how to meet new situations or to withstand the effect of long continued stress. In other words in the aged animal there is a breakdown in the mechanisms of integration of various organ systems essential in maintaining homeostasis.

Wound healing and tissue regeneration

It is common belief that the healing and repair of tissues is slower in old animals than in young. Although early experiments on animals tend to confirm this belief, Arey (2), Bourliere (12), and Du Nuoy (48) found no differences in the rate of healing of wounds in rats between the age of 10 and 30 months. Substances which inhibit the growth of cells in tissue culture have been observed in the blood plasma (28, 29, 93) of old animals. However, neither the nature of the substance nor the mechanism of its action have been identified. Reduction in the ability to form new tissue and the tendency to deposit collagen and fibrin in tissues may be regarded as part of the impaired homeostasis present in older animals. For instance, the rate of regeneration of liver tissue is greatest in embryos and diminishes greatly in old animals (18, 136). Similarly the rate of hypertrophy of the remaining kidney after unilateral nephrectomy is greater in young animals than in old (108).

This reduction in growth capacity with age is, however, not a general characteristic of all cells as shown by the high incidence of benign hypertrophy of the prostate in old men (125, 126), and the increase incidence of cancer in old age (9, 45, 129). In a total of 375 cases, Moore (125, 126) failed to observe hypertrophy of the prostate before the fifth decade. After this age, the incidence increased until at the ninth decade 75 per cent of the prostates secured from consecutive routine autopsies were hypertrophied.

The increased incidence of cancer in advanced age may also be taken as evidence of breakdown of regulatory mechanisms within the organisms which normally control cellular growth. In certain instances there is evidence that some of the controlling influences are endocrine in character; for example, studies of Huggins and his coworkers (78, 79) indicate that reducing the amount of male sex hormones by castration or by endocrine

neutralization through the administration of female sex hormones may retard the development of prostatic carcinoma and result in clinical improvement of the patient.

Susceptibility to poisons and toxic agents

Old animals are more susceptible to certain poisons and toxic agents than are young ones. MacNider (109 to 113) has shown that small doses of chloroform or uranium salts produced much greater liver or kidney damage in old than in young animals. It is also known that young animals are much more resistant to the toxic influence of anoxia. Respiration and reflex activities continue at lower oxygen tension and resuscitation after severe anoxia is more successful in young than in old animals (49, 50, 51, 65, 68, 167).

Responses to drugs

The action of certain drugs differs in old animals from that in young, for instance, histamine dihydrochloride, sulphapyridine, or pictrotoxin are less toxic to young animals than to old ones. On the other hand other drugs, such as morphine or ephedrine hydrochloride, are more toxic to young animals (31). Aged patients are more sensitive to drugs, such as digitalis, strychnine, etc., than are younger ones (15, 30, 41, 129). Dearing, Barnes, and Essex (41) for instance, have recently shown that pathological changes in the heart are more easily produced by small doses of digitalis in old animals than in young ones. Thus, the increase in deleterious effects of drugs and toxins in older animals offers additional evidence of reduced homeostatic capacities.

SUMMARY

In this chapter the thesis is presented that phenomena of ageing and death must be due to inability of the organism to maintain homeostatic conditions in its internal environment. Biochemical and physiological evidence has been presented to indicate that with increasing age the body is less capable of maintaining the constancy of its internal environment. Adequate regulation is dependent upon the effective coordination of the activities of many organ systems. With increasing age, more and more of the reserve capacities are secondary lines of defense against physiological displacements inherent in living must be called into play. The effectiveness of these systems can be assessed only through the application of a wide variety of stress tests under standardized conditions. Only through such tests can we obtain objective data on changes in reserve capacities with age.

Knowledge of the integration and coordination of organ systems subjected to stress is necessary if we are to devise methods and techniques,

for maintaining these adaptive mechanisms. It is well to emphasize that although our knowledge must be based on average figures, many individual exceptions are to be found. The evaluation of the causes for these wide individual differences is one of the major goals for future research.

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19

TEETH AND JAWS

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Loss of all of the teeth is the most striking oral symptom of ageing, although many less spectacular changes occur in the oral region as direct or indirect results of growing older. A mental picture of toothless old man or woman with reduced intermaxillary dimensions and a prominent chin (fig. 1) is associated by many individuals with the term "senile". Actually, disease is responsible for the loss of most teeth, and it is a mistake to assume that loss of teeth is an inevitable sequella of ageing (figs. 2 and 3).

The loss of teeth increases with each decade of life and although the causes of tooth loss are disease processes, the chronicity and persistance of the disease which lead to dental extractions make their results problems of ageing. Brekhus (1) showed that the number of missing teeth per person increases with each decade. Most of the loss of teeth in the 9,450 individuals studied was a result of periodontal disease or of dental caries. Brekhus compared, graphically, the loss of teeth from caries and from periodontal diseases (fig. 4). A similar study made by Allen (2) also showed the loss of teeth from caries to decrease proportionately with age, while the loss of teeth from periodontal disease increases as shown in table 1 adapted from Allen.

It is evident that as the age of an individual increases, the changes in the supporting structures of the teeth become more important and the relative importance of dental caries decreases. Brekhus has aptly stated that periodontal diseases "*take up the torch where caries drops it*". In spite of the discouraging statistical picture presented from Brekhus data,

which show that at age 70, 80 per cent of women and 70 per cent of men have lost all of their teeth, there is no justification for assuming such a condition to be inevitable (fig. 2). The discovery of truly preventive



FIG. 1. Senile atrophy of jaws. Note reduction of intermaxillary dimensions and prominence of chin. (From Thoma, K. T., *Oral Pathology*, C. V. Mosby Co., 1951.)



FIG. 2



FIG. 3

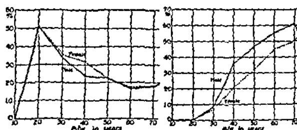
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lowering of alveolar bone crest level.

measures that seem to be closer to the realization of investigators, and the general employment of protective therapy, may reduce loss of teeth even through advanced age. As the disease processes are eliminated from the oral cavity, the true ageing changes will become of increasingly greater importance.

The problem of ageing in the oral regions will be considered in relation

to various structures: 1) the tooth proper (enamel cuticle and enamel, *dentin, pulp, cementum*), 2) *the periodontium (periodontal membrane and* alveolar bone), 3) the oral mucosa and related structures, 4) the maxilla, mandible, and temporomandibular joint. *In addition, the clinical signifi*cance of the ageing changes will be discussed.



sota Press, 1941.)

TABLE 1

Age	Teeth lost by caries	Teeth lost by periodontal disease	Total extractions
1-10	54 (85%)	0 (0%)	63
11-20	72 (63%)	1 (1%)	114
21-30	208 (73%)	21 (7%)	289
31-40	101 (44%)	118 (51%)	230
41-50	103 (40%)	148 (57%)	260
51-60	70 (26%)	186 (61%)	271
61-70	43 (40%)	60 (56%)	107
over 70	44 (49%)	46 (51%)	90

DENTAL TISSUES

Enamel and enamel cuticle

Enamel is the *only* calcified tissue of epithelial *origin* normally found in the body. One of its most *unique* and, *from the standpoint of ageing and* repair, one of the most important features of enamel is its lack of power *of regeneration. When the enamel has been formed, the cells of its forma*tive origin keratinize, calcify or disappear. The enamel is formed by the enamel organ, a derivative of the fetal oral epithelium. During the centrifugal apposition of enamel, the enamel secreting ameloblasts move outward to meet the outer epithelial layer of the enamel organ. After the

enamel has been aposed, the ameloblastic layer and the outer epithelial layer unite to form the united enamel epithelium, the inner portion of which calcifies or keratinizes and remains on the surface of the enamel except when removed by abrasion or disease. This structure is the primary enamel cuticle.

Bibby and Van Huysen (3) observed a membranous film present on practically all teeth and separable by immersion in acid solution. On teeth which had been erupted for many years "the film seldom shows an epithelial or keratinous structure such as has been described for Naysmyth's membrane" (enamel cuticle). The organic structures of the enamel surface seemed frequently to undergo a change resulting in pigmentation and an alteration in the enamel rod sheath. They suggest that this surface pigmentation may account for the darkening of teeth with age, a phenomenon ascribed by others to increase in the thickness of the dentin. These investigators also observed the formation of a thick, somewhat structureless brown layer on the outside of teeth. They assumed that it might increase resistance to decay. This is apparently different from the brown pellicle described by Manly (4) and Valloton (5), as forming on the tooth surfaces of some individuals using non-abrasive dentifrices.

Scott, Kaplan, and Wyckoff (6) have studied tooth surfaces by the replica method. They found cuticular structures existing on many teeth even after fifty years of age. Contrary to general opinion, cracks on the enamel surface did not increase with age (93% at ages 10–14; 95% at ages over 50). The percentage of teeth showing surface perikymata, enamel rod ends and an irregularity termed "stratification" reduced markedly with ageing. Since the reduction in all of these surface irregularities was more marked on the exposed surfaces (labial, lingual, and buccal) than on the proximal surfaces, it may be assumed that the polishing effects of food and dentifrices have important roles in smoothing enamel surfaces.

As a result of mastication, the enamel is subject to wear more striking than that seen in shadowed surface replicas. On the occlusal surfaces and at the proximal contact points attrition (mechanical wear during mastication) reduces the bulk of the enamel (fig. 5). The amount of use to which the teeth are subjected, the abrasiveness of foods and other materials (tobacco, betel) and the hardness of the teeth are the important factors which determine the degree of attrition of any individual dentition. Within certain limits, age governs the amount of use, dietary and other chewing habits (tobacco, betel) determine the degree of abrasiveness to which the teeth are subjected and, except for rare cases of amelogenesis imperfecta, dentinogenesis imperfecta or enamel agenesis, the hardness of the teeth is remarkably constant. A child with dentinogenesis imperfecta at age

14 may show more attrition than is usual at age 70, and a tobacco chewer or one living on coarse foods may greatly accelerate his rate of attrition

The effects of attrition may be more profound in regions other than the enamel. In dentin, sclerosis and secondary dentin may result, in the pulp fibrosis may be accelerated, the periodontium may be altered and the effects in the temporomandibular joint may produce local arthritis, otic disturbances and other symptoms. These various changes will be discussed with each of the structures secondarily concerned.

The process of attrition appears to be a normal ageing mechanism, and under ideal conditions the rate of loss of enamel cusps will bear such a relation to atrophy of the alveolus and gingiva as to maintain the clinical crown (the portion of the tooth external to the epithelial attachment of



Fig. 5. Attrition in 51 year old patient living on coarse diet

the gingivae) at a more or less constant height throughout life. Box (7) has directed attention to this phenomenon and in addition, by reference to the studies of Keith (8) and Campbell (9) on ancients' and aboriginals' skulls, concludes that the development of an edge to edge bite, to replace an overlapping bite, is a function of tooth wear. Linghorne (10) cites the removal of cusps and production of an edge to edge bite as functions of wear. These workers, as well as Begg (11), assign to the process of attrition the definite function of preventing periodontal disease. Campbell and Begg also note the attrition of interproximal spaces which may broaden the contact points and reduce the interproximal spaces thus leading to reduction of the interdental papilla. Wood (12) studied the effect of interproximal wear on shortening the tooth series in rhinoceroses and presents a lengthy bibliography on this age change. It is shown that, as a result of proximal attrition in man and other species, the mesial-distal diameter of individual teeth is reduced and the teeth drift mesially to reduce the total length of the tooth series.

The hardness and composition of dental tissues probably show little change from youth to old age. Differences in density (Boyd, Drain, and Deakins (13), and Berghash and Hodge (14)), birefringence (Harders-Steinhauser (15)) and composition (Bird, French, Woodside, Morrison, and Hodge (16)) have been demonstrated between deciduous and permanent teeth. That these should be considered as due to ageing is highly questionable, as they probably represent only intrinsic differences between two tooth series formed at different times. Karlstrom (17) from measurements on 81 teeth, concluded that enamel becomes softer with age and, from measurements on 48 teeth, that its specific gravity increases from youth to old age. Although the sampling errors were admittedly too great to draw conclusions, later he (18) attributed these changes to metabolic processes. Hodge (19), who has conducted intensive investigations of the hardness and composition of the teeth, has stated that there is little evidence to show much difference in the hardness of young and old teeth.

Chase (20) studied the maturation of 72 teeth of known age. There was no significant difference in the amount of enamel retained after decalcification in any decade of enamel age from the first to the fifth. He stated that enamel has probably reached the end-point of its maturation process at approximately three months after its initial deposition. McClure (21) found no variation in ash, calcium or phosphorus content of human enamel with either age or caries experience.

Many investigators have interpreted simple diffusion as evidence of metabolic activity. Since the tooth acts as a semi-permeable membrane situated between the pulp and saliva and can be penetrated by small ions and water (Fosdick (22)), penetration of enamel should not be considered as synonymous with metabolic activity in enamel. Nevertheless, the penetrability of enamel at different ages is important. Fish (23) found enamel of young dogs permeable to fluids by simple diffusion but this property was reduced in older dogs. He reported human enamel to be impermeable, for the most part, under the conditions of his study. Skillen (24) was unable to stain the enamel of freshly extracted teeth. Also using dyes, Bodecker and Lefkowitz (25, 26) have demonstrated penetration of dyes through the enamel of dogs and, to a lesser degree, of man. They have stated that maturity greatly reduces the permeability of enamel.

Radioactive isotopes have been used to study the possible metabolic activity of enamel and the penetrability of enamel. Studies by Chiewitz and Hevesy (27); Manly and Bale (28); Hevesy and Armstrong (29); Manly, Hodge, and Van Voorhis (30); Wasserman, Blayney, Groetzinger, and DeWitt (31); Volker and Sognnaes (32); McCauley (33); Volker (34); Wainwright and LeMoine (35); among others, have indicated that radio-

active isotopes are deposited in the enamel of living teeth. These studies show that the deposition of ions in enamel is feeble in comparison with that in bone and soft tissues and only about 5 to 10 per cent of that in dentin. It is probable that the changes seen in fully formed enamel are the results of physical adsorption or inorganic chemical combinations rather than the type of metabolic exchange encountered in cellular tissues. Nevertheless, Volker claimed that the evidence from studies with P^{32} in various animals indicates that the radio-phosphorus "metabolism" of dental tissues decreases with age. Wainwright and LeMoine, from investigations with radioactive urea on 14 freshly extracted human teeth, found little or no penetration in 4 teeth that had been erupted for 25 years or more and marked penetration in younger teeth. Again, this is evidence of penetrability rather than age. In support of the idea that permeability of enamel is lost with age, Adler, Straub, and Popovics (36) found the intravital uptake of fluorides lower in individuals over 20 years of age than in those under 18.

The relationship between dental caries and ageing is worthy of discussion, for caries is one of the two most important diseases that cause loss of teeth. Since the carious process is initiated as a decalcification of enamel, it is properly discussed with the enamel.

Hollander and Dunning (37), on the basis of examination of 12,753 individuals, found that the number of carious surfaces per person increases rapidly from age 17 to age 34 (about 1.75 new surfaces affected per year) and that the rate of cavity development slows down progressively beyond age 34. They found the process of decay measurably active even at age 50. These authors recognize two probable sources of error in their statistical data: fillings already present were not recorded as cavities and the number of attackable surfaces is reduced with age. Either of these would lead to an apparent reduction in caries rate.

Klein and Palmer (38) computed the relationship between tooth age and attack of the lower first permanent molar by caries and described a catalytic curve The fitting of this curve indicates that the yearly rate of attack is the same as all post-eruptive ages for this tooth, i.e., 19.03 per cent of the susceptible lower first molars are attacked annually. On the basis of 2.175 percentage of teeth attacked by caries during the 18th year, Sloman (39) computes that all teeth would be carious by age 46. On the basis of these data, *he concludes that there is a substantial decrease in* caries rate during middle life.

Schlack (40) examined 209 men upon an American man-of-war and reexamined them one year later. By accurate diagnostic methods, he found 0.56 new carious surfaces per man in age group 17–19 (82 men), 0.56 per man in age group 20–24 (91 men), 0.00 per man in age group 25–39 (41

men), 1.00 per man in age group 40–51 (5 men). This group is admittedly too small for drawing definite conclusions but suggests that direct repeated examinations may reveal valuable data.

Using bacteriological and chemical tests for caries susceptibility, Burrill (41) found the age of greatest susceptibility to be between the ages of 13 and 21 years, but he tested only 6 patients over 50 years of age. Hodge (42) found 1 year old normal and castrate female rats to develop rat caries (on coarse corn diet) more slowly than weanling rats. Braunschneider, Hunt, and Hoppert (43) also found older rats (100–150 days) less susceptible to the type of caries that rats develop than were young rats (35 days) on similar diets.

Bodecker (44) has classified caries into acute dental crown caries, chronic dental caries, and acute dental root caries. The latter type usually affects the teeth of individuals past middle age, often in previously non-carious teeth and probably as a result of carbohydrate degradation in dento-bacterial plaques formed on recently exposed root surfaces. A marked increase in caries activity in individuals past 50 to 60 years of age is often observed clinically. This may be the result of a combination of root exposure, i.e., newly susceptible areas, decreased salivary flow and a newly acquired desire for consumption of refined sugars. Each time refined carbohydrates, as sugar, candy, pastries, sweetened soft drinks or other forms, are taken into susceptible mouths, acids are produced in the small areas under dento-bacterial plaques and remain unbuffered for approximately 30 minutes. Obviously, if older individuals with susceptible areas acquire the habit of consuming such carbohydrates 6 to 9 times per day instead of at meal times only, they will double or triple their caries' activity. Even increased resistance to enamel or dentin solution in acid may not be great enough to affect this increased acid activity. In short, age appears to have only a passive effect on the carious process (Robinson (45)).

The feasibility of reducing caries susceptibility by applying fluorides to teeth of children is now well established (Easlick (46)), but its value in adults has been questioned. The results obtained by Klinkenberg and Bibby (47) on young adults indicate that topically applied fluorides may be as effective on the teeth of adults as with children. The effectiveness of artificial fluoridation of water on the teeth of young children and of adults, is now being tested in a number of communities. Unfortunately, as significant results were not anticipated in adults, only young children were included in the pre-experimental surveys of most of these communities, although adults as well as children consume the fluoridated waters.

The method of reduction in carbohydrate intake has been demonstrated by Jay (48) and others to offer a means of positive reduction in caries activity. The possibility of acquiring salivary immunity should not be

overlooked (Hill (49)). Brushing the teeth immediately after each consumption of refined sugar products has been demonstrated to reduce new cavity formation by 50 to 60 per cent (Fosdick (50)). This technique is as useful for the old individual as for the young. The possibility of reducing caries activity by dietary measures directed at increase in the mineral content of teeth is extremely remote (Robinson (51))

Erosion is defined as a condition of the teeth characterized by loss of substance beginning on the outer surface, progressing inward by a physicochemical process and leaving a smooth, polished surface (fig. 6) Its cause is unknown although many etiological possibilities have been conjectured *Since enamel does not repair itself, the prevalence of erosion, like that of* abrasion, attrition and caries, increases with age.

Abrasion is the mechanical wearing away of tooth substance by forces



Fig. 6 Dentifrice abrasion in man using a commercially available abrasive powder dentifrice Abrasion is in exposed roots

other than those of mastication. The most common type occurs in the root as dentifrice abrasion and will be discussed later. The harder enamel may be abraded by pipe stems, by sand in sandblasters, by the tube in glass blowers, by nails, tacks and needles in carpenters, upholsterers, carpet layers, tailors and seamstresses, and by bobby pins in beauticians and other women. These mechanical defects accumulate and are more common in older individuals.

Dentin

Dentin is a calcified tissue of mesodermal origin and since its chemical composition and crystalline structure are very similar to those of bone, it may be considered as modified bone. The chief points of difference, structurally, are the presence of tubules in dentin but not in bone and the presence of lacunae and osteocytes in bone but not in dentin. Physiologically, bone is resorbed and redeposited during life but dentin resorption is pathological, except during shedding of deciduous teeth.

Dentin consists of calcified fibrillar ground substance pierced by myriads of minute tubules (1 to 4 microns in diameter). The tubules of young teeth contain the processes of the odontoblasts, dentinal fibers, and the tubules possess a uniform translucency. In adult teeth many of the tubules may be completely calcified, producing apparent differences in their refraction of transmitted light. Dentin in which the tubules are dark to transmitted light is called opaque dentin; that with transparent tubules is called transparent or translucent dentin (Beust (52)). Beust (52, 53) believed the formation of transparent and opaque dentin to be a normal growth phenomenon which may be hastened by caries, erosion, trauma or other external stimuli. He objected to the term "dead tracts" in referring to opaque dentin because these areas are sclerosed and impermeable, rather than necrotic. The transparent areas he considered as representing a stage of transition between normal and opaque dentin.

Lefkowitz (54) has determined a definite age pattern for the development of this opaque dentin which he calls metamorphosed dentin, after Bodecker. The change occurs in the crown dentin at 15 to 19 years after eruption, in cervical dentin at 25 to 29 years and in the middle third of the root at 30 to 34 years. Metamorphosis proceeded normally in unerupted teeth. This dentin is less permeable than normal and less sensitive because of the lack of protoplasmic processes. In a chemical analysis of metamorphosed dentin, Ellison and Halpert (55) show a lower percentage of organic matter and a decreased percentage of calcium and phosphorus in the ash as compared to normal dentin in the same tooth. Ellison and Halpert postulate that the change is due to the deposition of some inorganic substance, the nature of which is as yet undetermined. Thomas (56) has shown that cavities can be cut in metamorphosed dentin without pain to the patient and suggests that this be kept in mind in preparing cavities for fillings. Hord (57) produced premature ageing of dentin by placing three per cent paraformaldehyde in shallow cavities in dogs' teeth without damage to pulp tissue.

The dentin beneath an area of enamel attrition develops a cone of opaque sclerosed dentin which has its base at the occlusal surface and its apex toward the pulp. This area has been named the attrition cone by Van Huysen, Hodge and Warren (58) who showed marked increase in roentgen-ray absorption in this cone compared to normal coronal dentin in the same tooth. In addition to forming the attrition cone, as the surface dentin is worn off, there is an increased deposition or irregular dentin at the apical portion of the pulp which tends to keep the dentinal thickness constant and prevent pulp exposure (figs. 7 and 8).

As the tooth becomes older, the thickness of the dentin increases due to continued deposition by the cells of the pulp. The dentin layed down

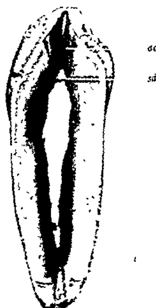
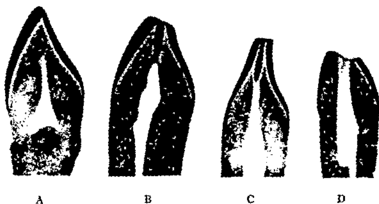


Fig. 7 Ageing changes in the calcified dental structures. Attrition of enamel with attrition cone (*ac*) and secondary dentin (*sd*) beneath area of attrition and sclerotic dentin.



after completion of the normal configuration of the tooth is secondary dentin. It is readily distinguished from the primary dentin by a sharp bend in the dentinal tubules and by a reduction in number of tubules which are much more irregular in size and course. Benzer (59) distinguishes sharply between physiological secondary dentin and that developing as a response to external stimuli. Normal physiological secondary dentin begins to form at an early tooth age. In multirooted teeth, it appears first on the floor of the pulp chamber, then on the sides and roof of the chamber spreading to the root canal. In single rooted teeth, formation is first in the crown then down the root canal. The major part of growth is completed by a tooth age of 20 years but continues slowly throughout life. This type of secondary dentin develops in unerupted teeth as well as erupted and can be accepted as one of the pure age changes of a tooth.

Localized areas of rapidly developing secondary dentin forms under areas of exposed dentin and is considered as a defense reaction of the pulp to irritation. The tissue formed is much less regular than physiological secondary dentin and has few tubules or sometimes is atubular It is found under areas of attrition, caries, fillings and exposed cervical dentin. The term irregular dentin has been applied to this type to distinguish it from the more regular secondary dentin. Van Huysen, Hodge and Warren (58) found the irregular dentin under attrition to vary in roentgen-ray absorption from 2.5 per cent more than that of normal crown dentin to 9 per cent less, and Hodge (60) found the microhardness of transparent secondary dentin to be 20 per cent less than that of normal coronal dentin in the same tooth. As the amount of secondary and irregular dentin increases, the size of the pulp is correspondingly reduced until, in elderly individuals or under pathologic conditions, the pulp may be reduced to a thread-like structure.

Using whole teeth, which are composed chiefly of dentin, Black (61) found the average specific gravity to gradually increase from 2.066 at 11 years of age to 2.109 at age 63. Lime salts, calculated as ash residue, increased from 62.26 per cent at 11 years to 64.56 per cent at age 63, while the water and organic matter showed comparable decreases. Black also found the strength of dentin reduced in older individuals. Crowell, Hodge and Line (62) analyzed whole teeth and reviewed the literature. On the basis of their own results they question whether maturation in teeth "is evidence of change in chemical composition". In a later study LeFevre and Hodge (63) reported a "remarkable constancy" in the composition of tooth substance and found little evidence of changes due to age in chemical composition. Although Black and Kuhns (64) using human material and Matsuda (65) using rats and Bernardi using bulls (66) reported

some changes in tooth composition with age, Hodge (19) believes there is little change between 20 and 60 years.

Fish (23) found an increase in calcium percentage, as calcium oxide, to vary between age groups 9–14, 30–45 and over 60. He reported an increase of 4.3 per cent of dentinal calcium salts of premolars between the 9–14 and 30–45 age groups. Between the age groups 30–45 and over 60 he found a loss of 2.5 per cent of the total dentinal calcium salts of incisors, canines, premolars and molars. Fish, however, was unable to modify the dentinal calcium by post-eruptive parathyroidectomy, calcium deficient diet, pregnancy, or excess intake of Vitamin D. Here again there are suggestions of changes in tooth composition with age and conflicting evidence of a constancy of composition unaffected by experimental interference with calcium metabolism.

The studies with radioactive isotopes indicate that the dentin has a much



FIG. 9. Erosion of enamel in upper incisors

higher rate of phosphorus metabolism than has enamel, but less than bone. Unerupted, partly calcified teeth approached the surrounding bone in content of P^{32} in the experiments of Volker and Sognnaes (32), whereas erupted teeth showed approximately one-fourth the P^{32} content of maxillary bone. These authors remark that the highest and lowest radioactive phosphorus depositions were in the youngest and oldest animals in their cat series. They believe this to be due to the amounts of tooth tissue exposed to circulating fluids.

Dentifrice abrasion may wear away the dentin but no commercially available dentifrices seem capable of wearing away the harder enamel (fig. 9). Manly (67) and Kitchin and Robinson (68) have shown that exposed root surfaces are readily worn by dentifrices, some being capable of wearing half way through a tooth root in less than 8 years. Of course, no tooth is susceptible to this disturbance until the root surface is exposed. Kitchin (69, 70) has shown the incidence of unprotected root surfaces increases from 58 per cent at age 20–29 to 95 per cent at age 50–59. Thus root abrasion by dentifrices is much more common in older age groups.

An interesting application of age changes in teeth is furnished by Gustafson (71) in an attempt to determine age of an individual by analysis of the condition of single teeth. A rough quantitative estimation is made of each of the following features: attrition, periodontosis, secondary dentin, cementum apposition, root resorption and root transparency (metamorphosis). In young individuals, closure of apex is also used. Accuracy of age determination is high, ± 3.6 years and increases rapidly when more than one tooth is used in the estimation. No single feature will permit accurate determination since each is so subject to variation.

In general, the results of chemical analyses of young and old dentin are inconclusive. It appears that the chief ageing changes in dentin are sclerosis of tubules (maturation?), increase in bulk, loss of strength, and possibly increase in specific gravity and mineral salts.

Pulp

The pulp consists of connective tissue occupying the central cavity in the dentin and is the remnant of the dentinogenic organ. It forms dentin and is the sensory tissue of the tooth. The framework of the pulp is a network of fibroblasts. It also contains undifferentiated mesenchymal cells, lymphocytes, histiocytes and modified connective tissue cells, the odontoblasts. The young pulp has a rich vascular supply, myelinated, and unmyelinated fibers of the fifth cranial nerve and, possibly, lymphatics.

The pulp undergoes marked atrophic changes with age. The syncytium of fibroblasts, which resembles mucoid tissue, is gradually transformed into a fibrous tissue with fewer cells. The blood vessels and nerves are reduced at the same time. The odontoblastic layer becomes vacuolized by the intercellular accumulation of fluid (fig. 10).

Kronfeld (72) described the regressive changes in the pulp as being initiated by the accumulation of fat droplets in the fibroblasts, odontoblasts and walls of the capillaries. Further regression is characterized by vacuolization of the odontoplastic layer and atrophy of the pulp tissue, both processes are characterized by decrease in number and size of cells and their replacement by fibers.

Pulp calcifications are found especially in older teeth. Diffuse deposits of calcium may be found in the walls of the pulp vessels of old people but more frequently well-outlined calcified bodies are present. The frequency of these pulp stones, pulp nodules or denticles has been studied by Hill (73) and William (74). Hill, in a series of 132 teeth, examined microscopically, found pulp calcification in 80 per cent distributed as shown in table 2. Similarly, William found calcifications in 87.2 per cent of 164 teeth examined microscopically. In only 15 per cent of these teeth could the changes be observed radiographically.

In addition to these changes in the tissues of the pulp itself, Bodecker (75) and Hess and Zurcher (76) noted the reduction in the size of the pulp chamber and an increase in the number of apical foramina due to continued deposition of dentin and cementum. Continued deposition of dentin may result in complete obliteration of the pulp cavity while cementum may close the apical foramina.

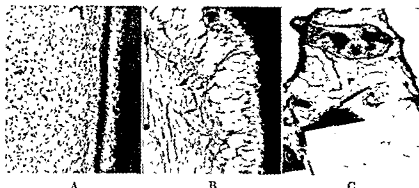


Fig. 10. Photomicrographs showing changes in the pulpal tissue A Pulp of young individual showing mucoid connective tissue and columnar odontoblasts B. Pulp of 54 year old male showing fibrosis of pulp and hydropic changes in the odontoblastic layer. C. Pulp of 72 year old female with marked fibrosis and calcification of pulp.

TABLE 2

Age	Number of teeth examined	Percentage with calcification
10–20	9	66
20–30	20	66
30–40	16	80
40–50	46	82 6
50–60	20	90
60–70	11	90

Cementum

Cementum is a calcified tissue which originates from the dental follicle. It serves as an attachment for the fibers of the periodontal membrane and *repairs injured areas on the root surface.* Because of this function of attachment the cementum, on a physiologic basis, can be considered as part of the periodontium. The cementum first formed in apposition to the *radicular dentin, primary cementum,* is acellular and appears structureless. It exhibits striations, paralleling the dentino-cemental junction, which represents incremental lines of deposition and lines at right angles

to the surface which are embedded Sharpey's fibers from the periodontal membrane. A secondary cellular type of cementum is found on the apical root surface and at the bifurcations of roots of molars and premolars. This cementum begins to form before the teeth are exposed to stress (Kronfeld (77)).

The secondary cementum is slowly and continuously deposited throughout life, a process indicated by the presence of incremental lines in the



FIG. 11. Secondary cementum at apical area of tooth root This cellular cementum is normally increased with age.

cementum. This cellular cementum closely resembles bone, differing chiefly because it is normally formed but not resorbed throughout life and because it seldom encloses blood vessels in anything resembling Haversian canals (fig. 11). As the cementum is deposited the cementum cells within the lacunae are well stained and fill the lacunar spaces while in the deeper, older layers of cementum the cells may be shrunken or the lacunae empty. In young teeth the secondary cementum is usually confined to the apical one-third or one-fourth. It extends more toward the cemento-enamel junction with advancing age. Thoma and Goldman (78) maintain that secondary cementum formation compensates for the continued eruption of teeth and prevents thickening of the periodontal membrane. Henry and

Weinmann (78B) have found small areas of root resorption increasing with age.

Excess formation of cementum, hypercementosis, occurs in some individuals. Efforts to correlate this condition with various diseases have been unsuccessful. There is some evidence that heredity may play a role (79), while arthritis seems unrelated (Sorrin (80))

The Periodontium

Periodontal membrane

The periodontal membrane is a connective tissue structure which acts as the attaching mechanism between the cementum and alveolar bone. It is the formative organ (periosteum) of the alveolar bone and cementum, serves as a sensory (touch) organ of the tooth, is a nutritive source for cementum, dentin and bone and supports the gingivae as well as the teeth (Orban (81)). The periodontal membrane includes bundles of collagenous fibers (principle fibers), indifferently arranged fibers, fibroblasts, osteoblasts and cementoblasts, osteoclasts, epithelial cells, blood and lymph vessels and nerves.

The periodontal membrane demonstrates marked changes under functional stress. Various studies have shown that the width of the periodontal membrane varies in different individuals, in different teeth of the same person and in different regions of the same tooth. Coolidge (82) has given the average measurements of periodontal membranes as:

Teeth in heavy function (44 teeth)	0 18
Teeth not in function (20 teeth)	0.13
Unerupted teeth (5 teeth)	0 15

In the same report Coolidge gave the average measurements of periodontal membranes as follows:

Ages 11-16 (83 teeth)	0 21
Ages 32-50 (36 teeth)	0 18
Ages 51-67 (35 teeth)	0 15

*Since function has such a profound effect on the thickness of the perio*dontal membrane it can be understood why Kronfeld (83) stated that age has no noticeable effect on its thickness. However, Coolidge's data in*dicates a reduction of the width of the periodontal membrane with age.*

As teeth wear at their contact points by attrition, they tend to migrate mesially (Wood (12)). This change is reflected by changes in the periodontal membrane, the fibers being distended on the distal and relaxed on the mesial side (Orban (81)).

Attrition gradually reduces the cusp height under normal usage and horizontal stresses are thereby reduced and with that change in stress to the vertical the work of the periodontium as an attaching apparatus is lessened (Linghorne (10)). The wearing down of cusps, then, must be considered of importance in maintaining the periodontium. The thinner periodontium and less active alveolar bone can tolerate this reduced horizontal stress, but if normal attrition does not occur along with normal involution of the periodontium, periodontal atrophy may be accentuated and may lead to loss of teeth.

Alveolar bone

Alveolar bone is a relatively thin cortical plate lining the tooth socket adjacent to the periodontal membrane. This compact layer of bone appears in x-ray pictures as a radiopaque line and is called the lamina dura. Between the alveolar bone and the external compact bone plates the supporting bone appears as trabeculae. These trabeculae, as they are arranged about the teeth with the alveolar bone constitute the alveolar process and are formed in accordance with the requirements placed on them by stress of mastication. The cancellous bone may be influenced by metabolic influences and ageing. In old age, as in nutritional deficiencies and normonal dysfunctions, the alveolar process may show osteoporosis. The alveolar bone proper is influenced more directly by function.

Interproximal attrition, with mesial drift, results in resorption of the alveolar bone on the mesial and new bone apposition on the distal (Noyes, Schour and Noyes (84)).

The alveolar margins of the alveolar bone are resorbed with age. Occlusal attrition may prevent excess stress on the reduced alveolar bone and serve to maintain the ageing tissues in physiological balance (Linghorne (10); Box (7)). However, if convex surfaces of the cusps have been reduced to inclined planes and the cuspal height has not been reduced by attrition, the stress of mastication may be too great for the atrophied alveolar bone and can lead to pathologic resorption with loss of teeth.

After removal of the teeth the now afunctional alveolar bone normally atrophies and the trabeculae of the alveolar process are rearranged under a new cortical bone plate to form the edentulous bony ridge.

Gingivae and epithelial attachment

The gingiva is attached to the teeth by the epithelial attachment (Gottlieb (85)). The area of attachment varies on different teeth, in different individuals and at different ages. The attachment at first is between the gingival epithelium and the enamel cuticle. In young individuals the bottom of the epithelial attachment is at the cemento-enamel junction,

approximately. With increase in age, the attachment shifts apically onto the root surface until it is entirely on the cementum of the root. Obviously, the attachment is now between epithelium and cemental surface. Thus the clinical crown increases in size and the clinical root reduces in size (figs. 12 and 13). The apical proliferation of the epithelial attachment and the accompanying changes in the periodontium are considered a continuation of the process of eruption.

The rootward growth of the epithelial attachment is accompanied by shortening and rounding of the interdental crests. The amount of alveolar bone loss is determined not only by the atrophy of the gingiva and occlusal movement of the teeth with attrition (Kronfeld (72)) and by lateral stresses produced in mastication (Box (7)) but also by the accumulated results of disease (periodontitis, periodontosis, traumatism). The rate of alveolar atrophy may vary greatly, the slower the rate the better the prognosis for the teeth. Although this atrophy of ageing is usually considered as physiologic, it is questionable whether it is inevitable in the disease free mouth. We have observed in our clinic many patients beyond the age of 70 who have gingival and periodontal structures suggestive of the usual picture at 30 to 40 years of age (figs. 2 and 3). The most striking difference between the usual atrophy of ageing and pathologic atrophy is that in the former, the gingiva, epithelial attachment and alveolar bone move apically at the same rate without pocket formation, while in the latter variations in the rate of tissue loss results in pocket formation (periodontitis, traumatism) or in general alveolar bone loss with drifting of teeth (periodontosis). Of course, periodontal disease produced by calcareous deposits, improper dental restorations, food impactions, infection, traumatism or systemic disease may accelerate or accentuate atrophy of ageing.

Oral Mucosa and Associated Structures

The salivary glands may regress with ageing, reducing the flow of saliva with relative or absolute xerostomia. This change may result in disagreeable oral sensations sometimes translated by the patient as burning tongue or glossalgia. It also interferes with proper retention of artificial dentures. It is highly probable that the decrease in salivary flow reduces the protection of the mucous membranes by the saliva. Such epithelial surfaces are more readily traumatized by the chemical products of tobacco, by the drying effects of alcohol, by hot foods and by spices. This may account for the greater occurrence of hyperkeratinized or leukoplakic areas in the mouths of older individuals. A similar change in the activity of small oral glands may lead to retention cysts in the labial, buccal or palatal mucosa. The atrophic secretory cells in these glands may cease to function temporarily and the duct epithelium fuses. Subsequent activity of these glands may

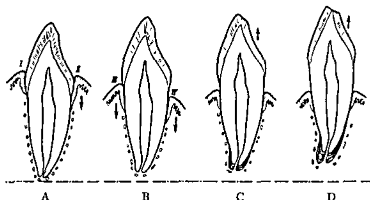


FIG. 12. Continued eruption of the tooth. A. *I.* The epithelial attachment is united with the enamel cuticle with its bottom at the cemento-enamel junction.

The height of the alveolus is reduced and secondary cementum is formed during this continued eruption (*C–D*). (From Gordon, S. M., *Dental Art and Dental Science*, Lea and Febiger, 1938.)

FIG. 13. Epithelial attachment in a young individual (*A*) and in a 54 year old

result in retention of fluid and the formation of small mucoceles. These are most commonly seen on the labial mucosa of older individuals as soft elevations about 0 5 to 1.5 cm. in diameter. Bauer (86) has observed fatty metamorphosis and the presence of onkyocytes (oxyphylic granular cells) in a study of 67 parotid glands from individuals 58 to 92 years old. These onkyocytes, derived from the ductal epithelium, are the characteristic cells of clear cell adenomas (onkyocytomas).

Sallay and Nador (87) found increased kallikrein (a hormone produced largely in the pancreas) present in greater amounts in the salivas of healthy older individuals and in young individuals with periodontosis. This work suggests that there may be important qualitative, as well as quantitative, changes in the salivas of older individuals.

Atrophic changes in the tongue may be characterized by loss of papillae. This smooth, bald or atrophic tongue is more common in elderly women (Prinz and Greenbaum (88)). The fungiform and filiform papillae are reduced or absent, and the circumvallate papillae reduced in number. The mucous membrane of the borders may be thin and parchment-like or the entire dorsal surface may be atrophic. Senile atrophy of the tongue should be differentiated from the glossitis of vitamin B complex, that of pernicious anemia and those accompanying other systemic disease. The elderly patient with atrophy of the lingual papillae may develop a phobia with symptoms of glossalgia or glossodynia. These are often difficult to differentiate from organic diseases but every possibility of anatomic or functional disease should be eliminated before the diagnosis of psychosomatic disease is made.

The mucous membranes of the entire mouth may appear thin and parchment-like in old individuals. This change may give the surface of the oral cavity a varnished appearance, and the sebaceous glands of the cheek may become more prominent (Fordyce spots). Xerostomia may contribute to this, as may vitamin B complex deficiency or hormonal dysfunction. A variant, seen most often in post-menopausal women, is desquamative gingivitis. In this disease the gingival epithelium may be raised in a bleb by blowing an airblast into the gingival sulcus. Engel, Ray and Orban (89) have demonstrated that the basement membrane is weak or absent and that the ground substance contains increased quantities of glycoproteins.

Pendleton (90), from a study of biopsies from regions under 39 dentures and 87 non-denture bearing edentulous areas, concluded that denture wearing increases parakeratinization and hornification. This is similar to the finding of Robinson and Kitchin (91) that massage with a toothbrush increases parakeratinization and keratinization of the gingivae. Pendleton also observed thickening of the stratum germinativum and subacute inflammation under dentures. *Resorption and repair of the bone underlying*

dentures and edentulous areas was noted with age apparently offering no barrier to process of regeneration and repair. Manly and Braley (92) found that chewing efficiency was greatly reduced by loss of individual teeth and that efficiency was reduced to from 88 per cent in complete dentitions to 35 per cent in denture cases. Manly and Vinton (93), from a survey of 100 denture wearing patients, found age and denture excellence the only two factors that influenced chewing efficiency, younger patients having better chewing performance with artificial dentures. Apparently, retention of natural teeth is highly important, and when teeth are lost clinically efficient dentures are valuable.

Cancer of the oral cavity should not be overlooked as a problem of ageing. Malignant tumors of the oral cavity are relatively infrequent in *females, but this should not be construed to mean that they are of no*

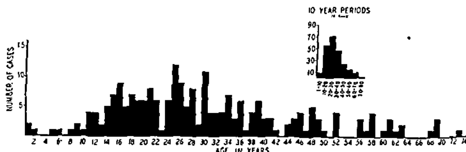


Fig. 14. The age of onset of 222 cases of ameloblastomas. (From Robinson, Arch. Path., 23, 831-843, 1937.)

importance in women. Women with Plummer-Vinson syndrome are generally believed to have a high susceptibility to oral cancer. Dublin (94) reported that 7 per cent of fatal cancers in men are in the oral cavity. Robinson (95) has estimated that as many as 7,500 people may die annually in the United States from cancer of the oral region. Most of these are in *the later decades of life. Although Bernier (96) has reported that cancer* of the lip may occur in young individuals, most oral malignancies are not *observed until after the fortieth year and many not until after the sixtieth* year (Darlington (97)). The ameloblastoma, a neoplasm of odontogenic origin, has a lower age incidence. Seventy per cent of 222 cases had their onset between the tenth and thirty-fifth year (fig. 14), although one was [illegible]

be taken to observe good oral hygiene, smooth rough tooth edges and correct ill-fitting restorations, especially in older people.

Maxilla and Mandible

Changes in the form and size of the bones of the face in old age and especially in senility are so obvious that they have become symbols of the general decline imposed on all who live past man's allotted time (fig. 1). The wrinkled skin, the thin flabby muscles, the up turned chin approaching the sharp pointed nose make a sad caricature of the features found in prime of life. Still, many pass the old age period and enter senility with but slight outward evidence of slowing vital processes. The question then arises, how much of this facial change is physiological and how much due to preventable pathologic imposition.

The two bones most responsible for height and depth of face are the two tooth bearing bones, the mandible and maxilla. The alveolar processes of these, intimately associated with the teeth, are the most variable elements. These processes form with the developing teeth and are removed as the teeth are lost. Growth of the maxillae and mandible and consequently of the face has been shown to proceed in a rhythmic manner associated with the development and eruption of the dentitions (Krogman (99)). The observation of Hellman (100) and of Goldstein (101) also indicate such rhythm. Hellman (102) in summarizing growth of height gives three main sources: moderate increase in dimension of upper and lower face, greater increase in subnasal and lower molar region due mainly to development of alveolar process and development of dentition. In old age major changes are similarly brought about by the loss of teeth and alveolar processes and attendant (or resulting?) changes due to change of position of the mandible and loss of muscle tone. The answer to the question then becomes another: is tooth loss physiological?

The maxilla shows little change in uncomplicated old age. The bone is thinner and the sutures tend to fuse. Tooth loss, however, followed by loss of alveolar bone causes a marked diminution of height and some changes in the size and shape of the maxillary sinus. Loss of width and depth are also seen in senility following alveolar bone loss.

Torus palatinus is a bony protuberance along the median line of the hard palate in the region of the union of the palatomaxillary sutures. The torus palatinus is usually considered a postnatal hyperostosis of the palatine processes. The relationship between the age and occurrence of the lesion is given by table 3 adapted from Miller and Roth (103). The lesion may interfere with proper placement of artificial dentures but usually has no other clinical significance except its occasional confusion, diagnostically, with palatal salivary gland tumors. Torus mandibulare is a similar hyperostosis occurring on the inner surface of the mandible in the premolar region. These tori usually are bilateral and lobulated. Aside from their interference with denture placement, they are not significant.

The classical description of the mandible in old age is also based on its appearance after tooth loss. The body is greatly decreased in height by loss of alveolar process leaving the mylohyoid ridge at or just below the upper surface. The mandibular canal is near the alveolar surface and the mental foramen appears near, or even on, the alveolar surface. The ramus is narrowed and thinned with a marked diminution of the muscle attachments. The angle of the ramus with body is increased and approaches the angle of the infant. All of these changes are associated with tooth loss and consequent loss of stimulus of physiological activity.

Goldstein made accurate craniometric measurements on 50 men of an average age of 74 years. All facial measurements showed diminution when compared to young adults. However, the relation of the angle of the mandible to the auditory meatus remained stable and the auriculo-menton

TABLE 3

Age	Number of patients examined	Percentage with torus palatinus
0- 5	80	2.5
5- 9	80	25.0
10-19	160	23 8
20-29	160	23.7
30-39	160	28.7
40-49	160	27 5
50-59	160	30 0
60-64	80	30.0
Average	1,040	24.2

distance changed very little. He associates this lack of change with change in the angle of the ramus. No relation between loss of teeth and change in length of mandible in old age is given. Hellman found similar changes in measurements on the skulls of American Indians. Loss of one half of the tooth height or loss of teeth were used as age indications. Hellman, however, stresses the fact that only a small change in obtuseness of angle occurs on observation which may be associated with the greater number of teeth found in his specimens compared to the expectancy in the men observed by Goldstein. The comparative slight loss of face depth at the mandible compared to that of the maxilla would explain the apparent lengthening of lower face (mandibular) in old age. Wrinkling of the skin and formation of sulci are associated with loss of intermaxillary dimension as well as loss of elasticity and fat.

Thompson (104) disputes the concept of change in face height with loss of dental and supporting structure. On the basis of a large number of cephalometric radiographs of the same individuals, he comes to the con-

clusion that the mandible assumes a relationship to the head by the third month of life that does not change subsequently. This relationship is determined by muscle balance and is not affected by growth or loss of teeth and supporting structure. Change in facial appearance with tooth loss is ascribed to loss of support of lips and cheeks. This rest position rather than occlusion is the necessary guide to proper dental restorations. Although Thompson's study is thorough and the evidence convincing, it is so much at variance with other observations that further study of this kind should be made. It is probable that a compromise between this concept and the results of previous observations will be found.

Change in angle of the mandible has been definitely shown to be related to tooth loss. Keen (105), from measurements on 127 skulls and radiographs of 135 living persons, found no evidence of increase of angle with age but a definitely greater angle in edentulous individuals. He believes that immediate denture service may help to preserve the angle but not to the extent indicated by Rogers and Applebaum (106) who have shown that maintenance of proper intermaxillary dimension by correctly fitted dentures or other restorations preserves the adult type of ramus and angle. They stress the importance of muscle tone in preserving the normal structure of the mandible. Even slight closure of the bite is shown to reduce the length of the muscles of mastication, except the external pterygoid, and consequently weakens these muscles. MacMillan (107) demonstrated this atrophy of the muscles of mastication and the areas of attachment in his dissections and models of the masticatory apparatus. Stuntz (108) has shown the importance of function in determining change in the mandibular angle in infancy. Lack of function in old age apparently has the reverse effect and the angle approaches that of infancy, although the observations of Hellman indicate that the change is much less than commonly believed.

Figure 15 shows four mandibles illustrating variations in form *A*, age approximately one and one half to two years, with only partially erupted deciduous dentition, has an angle of 135 degrees on the left and 131.5 on the right. This is near the upper limit reported by Stuntz for this age. *B*, the mandible of a well developed 52 year old negro male, has a complete dentition with mild attrition. The alveolar process is well developed showing only slight recession. The angle is 120 left and 123.7 right. *C* and *D* represent the edentulous condition with almost total alveolar resorption. A sharp alveolar ridge remains on the anterior of *C*, the mandible of a 69 year old white male. Very small muscle attachments are shown on a narrow ramus. The mandibular angle is 128 5 left and 130.5 right. The angle of *D* is 119.2 although it is from a 74 year old male. Muscle attachments are well developed on a ramus of good size and proportions. Another

edentulous mandible (not illustrated) from a white male aged 53 has an angle of 140 degrees. The form and angles of these mandibles from the Department of Anatomy of Washington University School of Dentistry seem to bear out the contention of Rogers and Applebaum and of Keen that age has less effect on change in the mandible than loss of dimension

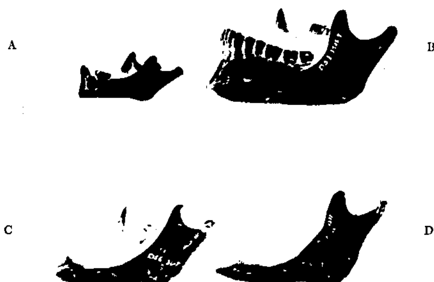


Fig. 15. Variations in form of mandible. A, mandible of child 1½ to 2 years of

Slight increase is shown in C.

and function. Brodie's (109) statement concerning the lack of change in mandibular angle has been nicely interpreted by Sicher (110) as a difference in terminology. Brodie's angle, at the gonion, is apparently stable.

During the past few years a great deal of interest has developed in symptoms associated with disturbances of the temporomandibular joint. These disturbances are not limited to older individuals but may occur at any time. However, since they have been associated with tooth loss and improperly fitted restorations, they tend to be more common in old age.

Costen (111) described a group of symptoms in individuals with edentulous mouths and marked overbite. He observed impaired hearing, "stuffy" sensation in the ears, tinnitus, dull ear pain, dizziness, headache, burning tongue, throat and nose.

Diagnosis of the condition is established by lack of molar teeth or badly fitting dentures permitting overbite; mild catarrhal deafness and dizzy

TABLE 4

Relationship of certain oral conditions and age

	Causes	Role of Ageing
Dental caries	Decalcification of enamel and dentin by acid produced by bacterial action on carbohydrates	Caries persists as long as teeth are present Root caries may present problems in older individuals
Attrition	Wear of contacting surfaces in mastication	Time, habits, physical properties of food, condition of teeth influence. More marked with age
Abrasion	Wear on tooth surfaces by forces other than mastication	Increase time of exposure and lack of enamel repair accentuate in older age groups
Erosion	Unknown	Time and lack of repair accentuate in older age groups
Periodontosis	Degenerative changes in periodontium	Unimportant except for greater prevalence of degenerative diseases in older individuals
Alveolar atrophy	Ageing and stress	An important and primary cause
Periodontal traumatism	Physical trauma	Alveolar atrophy and tooth loss may accelerate
Oral cancer	Unknown (trauma contributes)	More common in older age groups
Hyperkeratosis and leukoplakia	Trauma (chemical, physical, etc.)	More common in older age groups. Xerostomia a possible contributing factor

spells both improved or relieved by inflation of tubes; tenderness of mandibular joint to palpation; marked comfort when flat object is placed between jaws; and presence of typical headache when eye and sinus conditions are ruled out.

Pain in various regions is explained by pressure on the auriculotemporal and chorda tympani nerves by the displaced condyle and by pressure on the dura through the thinned bone of the fossa. Ear symptoms are explained in part at least by pressure on the eustachian tubes by compression of contents of infratemporal fossa or lack of contraction of tensor palati muscle

(Harris (112)). Relations of deafness to joint disturbance have been strongly questioned.

Goodfriend (113), Costen (111, 114, 115), Harris (112), Kallenbach (116), Higley (117), among many others, have discussed the effect of loss of vertical dimension on the joint. Many of the originally described relationships held responsible for the symptoms have been disproven. Sicher (118) has given an excellent review of the anatomical relationships of the mandible that may have an influence in Costen's syndrome. His conclusions are that nerve inpingment, closure of the eustachian tubes and destruction of the tympanic plate are not possible results of mandibular overclosure, but that breakdown of muscular balance is followed by changes in the joint leading to a well defined picture of deforming arthritis of traumatic origin.

Bauer (119) also found that functional traumata of the temporomandibular joint promotes the development of *osteo-arthritis deformans*. He was able to examine histologically the joints of a number of individuals of known history. Subjective symptoms were absent in some cases where the unbalanced action had led to complete destruction of the articular disc.

Markowitz and Gerry (120, 121), however, in a study of 700 unselected individuals found osteo-arthritis to be relatively rare. Twenty per cent of the group examined were found to have temporomandibular disease. Abnormalities in occlusion were the chief factors in the development of diseased conditions, complete loss of teeth seems to be a less important factor. Correction of occlusion prevents further destruction in the joint. The group examined by Markowitz and Gerry had a high proportion of comparatively young individuals which may explain some of the differences in their findings compared to others.

A review of the literature emphasizes the confusion surrounding the joint and its disturbances. Too little is known of the part played by congenital factors. Psychological factors also seem to play an important part at least in subjective symptoms. Evidence is definite that disturbances of occlusion and loss of dimension lead to degenerative changes which may produce distressing or even disabling symptoms. Early correction of masticatory imbalance or loss of dimension may prevent destruction or relieve symptoms. As in other conditions associated with the dental apparatus, prevention is easier and more effective than correction.

Summary

There are definite changes, in the teeth and associated structures, which can be attributed to the normal process of ageing. The composition of teeth is apparently influenced less than most other tissues of the body.

This is readily rationalized when the relatively lower metabolic rate of these hard tissues is considered. Changes in the pulp are more extensive and parallel regressions in other connective tissues of the body.

The process of attrition has an important function in maintaining physiologic balance in the periodontium. The reduction of the cusp height reduces lateral stress and prevents undue stress on the atrophic alveolar bone The pulp and dentin react to attrition with formation of sclerosed and secondary dentin. Attrition may also hasten fibrosis and calcification of the pulp.

The continued apical proliferation of the epithelial attachment affects the height of the alveolar bone crests and, in part, controls the periondontium. The ultimate outcome of this 'continuous eruptive process' is, theoretically, the exfoliation of teeth in old age. Many factors influence the recession of the gingiva and alveolar atrophy, indirectly controlling the fate of the teeth.

Caries of teeth remains as a problem even in elderly individuals but its importance is relatively reduced. Periodontal diseases become of increasing importance in older people. As dentistry controls or prevents caries, these diseases of the supporting structures will continue to demand greater attention so that in an older dental population the emphasis may be changed from treatment of hard tissues to soft tissue and alveolar therapy. Diseases of the periodontium may affect general health and hasten degenerative changes. It is a sad commentary that at age 40, 18 per cent of the American people need complete artificial dentures, at age 50 the need is increased to 28 per cent and at age 60, 40 per cent have lost their natural teeth (Walls, Lewis and Dollar (122)). Dentistry now has two great problems: To replace the teeth lost by caries and periodontal diseases and to find means of reducing tooth mortality for coming generations.

Changes in the jaws and face associated with old age are primarily consequences of reduction in size (attrition and tooth loss) and function of the masticatory apparatus. Many of the facial evidences of old age may be prevented by proper care, or replacement, of teeth Disturbances of the temporomandibular joint are commonly the result of mutilated or lost dentition in older individuals. Restoration of intermaxillary dimensions by artificial teeth or splints may relieve the distressing symptoms in this syndrome.

Anomalies of the teeth and jaws occur in at least fifty per cent of our population, and their sequelae are highly significant for health. Failure to recognize these facts has resulted in needless endurance of preventable lesions of the dental and other systems by older people. A more careful consideration of these anomalies is urgent. Simon's (123) concept of what constitutes a normal, anatomically correct denture, including its cephalic

relationship, has provided a rational basis for such treatment. Comprehensive diagnostic data are essential in making accurate diagnosis of denture mutilations, especially if they occur in anomalous dentures.

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20

DIGESTIVE SYSTEM

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Chicago

INTRODUCTION

A question of prime importance to the ageing person is the likelihood of death from disease of the digestive system. Although mortality statistics are not conveniently grouped so as to answer such a question accurately, the following rough comparisons are possible. Death in persons above 45 years of age is about as frequent from all diseases of the digestive system (7.0 per cent) as from chronic nephritis, slightly more frequent than from cerebral hemorrhage and paralysis, and about one-third as frequent as death from diseases of the heart. The relatively high rating of the diseases *of the digestive system as a cause of death is due principally to the fact* that cancer of the digestive organs is so prevalent. Cancer of the stomach, liver, gallbladder and bile ducts comprise almost one-third of the total of all forms of cancer. Two and six-tenths (2.6) per cent of all deaths are due to cancer of the stomach, liver and biliary passages. In addition, 13.6 per cent of all forms of cancer arise from the peritoneum, intestine, colon and rectum, and comprise 1.1 per cent of total deaths (1). To this should be added cancer of the buccal cavity (3.1 per cent of all forms of cancer and 0 25 per cent of deaths from all causes) and also of the pancreas. Thus, at least one-half of all forms of cancer which cause death arise in the *organs or tissues of the digestive system,* and *account for more than one-*half of the deaths due to diseases of the digestive system in persons above 45 years of age.

Some important sex differences exist. Cancer of the buccal cavity is six or seven times more frequent in males. Cancer of the stomach in males causes more than twice as many deaths as cancer of any other organ, and ranks second only to the uterus in females. According to Ewing (2), cancer of the gallbladder affects four women to one man. This accounts for the

higher incidence (about 22 per cent) of deaths from cancer of the liver and biliary passage in women, as is revealed by mortality statistics which do not separate deaths due to cancer of the liver and of the biliary passages (1).

Hepatic diseases rank next to cancer among diseases of the digestive organs as a cause of death in persons above 45 years; they account for about 1.6 per cent of deaths. Cirrhosis of the liver heads the list (about 0.9 per cent) and causes death in males about twice as frequently as in females. The death rate from biliary calculi (0.33 per cent) is about the same as the total from the other hepatic diseases (0.38 per cent), cancer and cirrhosis being excluded, and causes death about three times more frequently in females than in males (1).

Ulcer of the stomach and duodenum as a cause of death in the mature adult ranks third in importance among the diseases of the digestive system. Ulcer of the stomach causes death more frequently than ulcer of the duodenum, although the latter occurs more frequently. Both types of ulcer occur more frequently in males and cause more deaths in males. Deaths from these diseases do not become numerically important until after the age of 35, after which they increase up to the age of 75 (1).

Other fatal conditions due to disturbances of the digestive system that increase with age are intestinal obstruction, diverticulitis of the colon, and pernicious anemia. Hernia, one of the principal causes of intestinal obstruction, increases with age. Diseases of the pancreatic acinar tissue other than cancer rarely cause death. Deaths from diarrhea and enteritis, which occur for the most part in the years under 5, show an increase above the age of 55 (1).

It will become evident from the discussion to follow that deaths from disturbances of the digestive organs are usually due to diseases which do not represent a wearing out or ageing per se. In other words, most elderly persons die with a digestive system which, when not locally altered by cancer or by a toxic or an infectious process, is capable of functioning beyond the ordinary life span. This will be demonstrated by an analysis of the available evidence pertaining to the development, maturity and involution of the functional activities of the digestive organs. In such an analysis it is necessary to attempt to distinguish between the functional and structural changes due to ageing per se and to disease. In fact, the chief purpose of this chapter is to summarize what is known concerning the functional and structural changes due to ageing.

Salivary Glands

Anatomy

Data on the growth of the submaxillary gland have been provided for the rat by Donaldson (3), but the effect of age has not been determined.

In the human, Scammon (4) has found that the salivary glands increase about three times in weight during the first three months, and about five times during the first two years after birth. The connective tissue and ducts are relatively more plentiful than the parenchyma in the salivary glands of the infant. The glands do not become histologically typical of those of the adult until the end of the second year According to Warthin (5), the salivary glands of aged persons are atrophied, but he presented no decisive evidence. Goodpasture (6), who studied the histology of the submaxillary gland in fifty old stray dogs, found degenerative changes which occurred most uniformly in the cells lining the intermediate ducts. These cells are considered to be the chief contributors of water to the saliva by Stormont (7). Their degeneration may explain the observed reduction in the volume of saliva secreted by the aged.

Hamperl (8) has reported that numerous large cells with acidophilic granules in their cytoplasm and pyknotic nuclei may be found in the salivary glands of elderly people. He has termed these cells "oncocytes". Up to the age of 30 years, these cells are found only in occasional cases, whereas after the age of 70 years, they are invariably present in considerable numbers. Although Steinhardt (9) reported changes which did not conform to the description of "oncocytes", Hamperl (10, 11) has reaffirmed their existence.

Schramm (12) and Yamaguchi (13) called attention to increased amounts of fat in the salivary glands of persons older than 60 and Andrew (14) found marked fatty degeneration of the parotid gland of senile rats (700 days and over). Andrew (14) also found "oncocytes" in the glands of senile rats and he confirmed Hamperl's finding that these cells undergo amitotic division. Andrew (14) considered the oncocytes to bear important similarities to malignant cells.

Salivary secretion

Ptyalin is present in the mixed saliva of newborn and even of prematurely born infants. Its concentration increases during the first year, at the end of which it usually reaches the concentration found in young adults (15, 16, 17).

The only data available, which render a comparison of the salivary secretion of the young and old adult possible, are those provided by Meyer and his collaborators (18, 19, 20). Their observations show clearly that the output of saliva and its ability to digest starch is diminished after sixty years of age. Freeman (21) found no significant change in pH with age; he made the interesting observation that in 63 per cent of 27 edentulous subjects the reaction of the oral secretions was neutral or alkaline.

In the young adult at least 60 per cent of the cooked starch of a meal,

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Anatomy

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Gastric secretion

Considerable evidence is available concerning the relation of the acidity of the gastric contents after test-meals to age, especially in those decades above the second. Little evidence is available regarding the volume output and the peptic activity of gastric juice in the various age groups.

It is established that at birth the gastric mucosa of most mammals is differentiated sufficiently to secrete acid gastric juice Concentration of acid and pepsin is lower than found later (35). The stomach of the premature infant secretes acid juice (36, 37), and the gastric glands of fetal cats and dogs shortly before term respond to histamine (38). The mechanisms for the gastric and intestinal phases of gastric secretion are ready to function at birth, and the mechanisms for the cephalic phase (appetite secretion) become functional during the first year (39, 40).

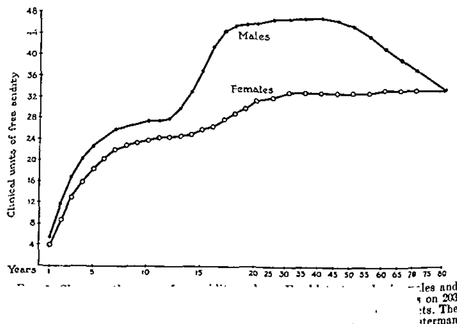
Wolman (41) has exhaustively reviewed the literature on gastric secretion in infants and children. It is well established that the acidity of the gastric contents of new born infants and sucklings is low. The number of studies with histamine is too small to establish reliably the incidence of absolute achlorhydria in infants. Izumita (42) using a test-meal, which does not constitute a reliable test for absolute anacidity, found three instances of achlorhydria among 52 infants varying in age up to 72 hours. Five instances of apparent achlorhydria were found among 36 sucklings up to 12 months of age. Ritter (43) found no free acid in the resting secretion of 4 out of 36 unfed newborn infants one-half to 14 hours after birth. Several authors (43, 44) have pointed out that higher acid values are found in the first few postnatal days than in the subsequent month or longer. Cutter (45) is the only one to report on histamine stimulation of newborns. No generalizations can be drawn because he studied only 9 infants.

A study of 330 children, ranging from 5 to 17 years, by Wright (46) and Klumph and Neale (47), who used a test-meal, yielded three probable but not proven cases of anacidity. The average acidity was lower than that of the adult. In the subjects studied by Klumph and Neale, the average free acidity did not begin to approach the adult range until after 4 years of age.

Actual data (48, 49, 50) on the results of histamine tests are available on only 63 children ranging from 0.5 to 14 years of age. No instances of achlorhydria are reported. It would be important to have data on a larger series of children to settle the question whether congenital or hereditary absolute achlorhydria ever occurs. *It is certain that most of the cases of*

anacidity or achlorhydria that occur in later life do not date from birth. However, it is apparent from the histamine and test-meal data that a wide range of variability in response occurs in early life. The high and low secretory responses that occur in adults also occur in children. A high or low *response is apparently a quality inherent in an individual at an early* age.

The mean free acidity resulting from an Ewald meal has been determined from data in the literature by Vanzant and her collaborators (51,



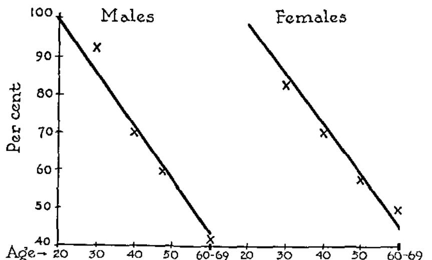
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52). The significant features of the data may be observed by referring to figure 1. Analogous data are presented by Segal, Marks and Kantor (53).

Similar data obtained by means of the histamine test are not available on a group large enough to give reliable results for the age group under 20 years. However, Polland (54) provides valuable data for the various decades from 20 to 70 years. When the mean acidity alone is considered, the instances of achlorhydria being excluded, it is evident that a decline occurs with age in males but not females. This result is analogous to that obtained with an Ewald meal (fig. 1). However, the histamine test permits a fairly reliable estimate of the volume of juice secreted as well as the acidity. An analysis of the data on volume shows that females secrete less juice at all decades above 20 years than males, and that the volume of juice decreases significantly as age advances. Knowing both the volume

and acidity of the juice secreted, it is possible to estimate the total amount of acid secreted at each decade. When this is done, an important fact becomes apparent, namely, that with advancing age a similar percentage decrease in acid production occurs in both sexes (fig. 2). If volume is not considered, it would appear that acid production decreases with age only in male subjects, as is indicated by the observations of Vanzant and her collaborators (fig. 1).

It has been definitely demonstrated that the incidence of achlorhydria increases with advancing age. This is well illustrated by the data (table 1)



[illegible] (data from Polland, 54).

obtained by Ewald test-meals and compiled by Bloomfield and Polland (55). It is confirmed by the data on histamine tests obtained by Polland (table 2) on 644 "normal" subjects. As might be expected the percentage of achlorhydria is less with histamine than with the Ewald test-meal.

A sex difference in the occurrence of achlorhydria has been observed by a number of investigators. Vanzant's data revealed achlorhydria to be present in 17.4 per cent of females and 12.9 per cent of males; Polland's (table 2) in 14.2 per cent of females and 10.8 per cent of males. Although the total incidence of achlorhydria is greater in females than males, the increase in achlorhydria with age is greater in males. The low mean acidity of females is apparently related to a higher general incidence of achlorhydria; and when the mean acidity of the males begins to decline after the

ritating substances. It is well known from experimental and clinical observations that nutritional deficiency, strong irritants and most infectious diseases produce a temporary achlorhydria. Continued or repeated insults, as with alcohol for example (63, 64), may produce atrophic gastritis with achlorhydria. The view of Einhorn (65) that achlorhydria is or may be neurogenic in origin has its adherents among clinicians (66, 67, 68). In this connection, it is of interest that Schnedorf and Ivy (69) studied eight monkeys which manifested achlorhydria to histamine for a period of from two to eight months. They found that after one or two doses of mecholyl, a parasympathomimetic drug, the stomach of the monkeys became responsive to histamine.

Because of the numerous uncontrollable factors which may operate in man and contribute to the development of achlorhydria and chronic atrophic gastritis, it would appear that much can be contributed to the problem of the effect of age on the morphology and secretory activity of the gastric glands by carefully performed experiments on laboratory animals.

The appetite secretion and the peptic activity of gastric juice is diminished after the seventh decade (19). The decrease in appetite secretion may in part be due to the decrease in taste that is associated with a diminution in the number of taste buds in ageing.

The consequences of achlorhydria

It is well known that many persons may have achlorhydria for years and remain in good health. The effect of the condition on the life span is unknown. On the basis of experimental studies on animals, persons with achlorhydria should be more disposed to gastrointestinal infections because of the loss of "sterilizing" action of gastric acid (70); they should be more prone to develop a hypochromic microcytic anemia because of the role that gastric acid plays in the absorption of iron (71, 72); and, they, especially growing children, should manifest defective calcification of the bones (73). Subacute combined degeneration of the spinal cord and pernicious anemia do not occur in animals rendered achlorhydric or achylic by total gastrectomy (71). In man it is known that achlorhydria (a) occurs almost constantly in pernicious anemia and subacute combined degeneraation of the spinal cord, (b) is frequently associated with hypochromic microcytic anemia, and (c) is sometimes associated with diarrhea and vague digestive complaints (74). The treatment of achlorhydria and its association with various diseases, such as allergic disease, certain dermatoses, glossitis, and rheumatoid arthritis has been reviewed by Oliver and Wilkinson (68).

Atrophic changes of the mucosa of the tongue are apparently more

frequent in elderly persons with achlorhydria than in those with normal acid values (75). This is more related to dietary deficiency than to achlorhydria (76). The relation of senile osteoporosis to anacidity is uncertain.

Pernicious anemia

It appears to be well established that pernicious anemia is at least in part due to a functional disturbance of the gastrointestinal tract. The stomach and probably the intestine secretes an "intrinsic factor" which acts on an "extrinsic factor" in the food so as to provide an "essential substance" for the normal maturation of red blood cells or for the prevention of pernicious anemia. The process of ageing, or factors contributing to an *atrophy of the gastrointestinal tract, may tend to decrease the elaboration* of the intrinsic factor; and hence, an increase in the incidence of pernicious anemia would occur with ageing. Recent evidence indicates that vitamin B_{12} is the extrinsic factor and that the function of the intrinsic factor, the nature of which is still unknown, is to aid in the absorption of the extrinsic factor.

Achlorhydria is of great diagnostic importance in pernicious anemia (77, 78, 79). In some instances it is known that achlorhydria may be present for many years with or without pernicious anemia resulting (80). Yet it is certain that the incidence of pernicious anemia, like that of achlorhydria, increases with age.

The results of a study of 1071 cases by Cabot (81), show that the disease is between six and seven times more common after the 35th year than before, and is rare under the age of 20 years. This is confirmed by data provided by Davidson and Gulland (79) and is supported by mortality statistics (1).

Does a sex difference exist in the incidence of pernicious anemia as it does in achlorhydria? The clinical reports vary widely in regard to the sex incidence of pernicious anemia. In practically every report the male and female population of the clinic from which the report comes is not considered. So, *in some instances the males with pernicious anemia markedly* outnumber the females; for example, Cabot (81) found that the disease was almost twice as common in males. In the anemia clinic of the Cook County Hospital, Chicago, from June, 1931, to December, 1937, 490 patients with the disease were diagnosed and responded to liver therapy. *Of these, 255 were males and 235 females. However, when the sex ratio is* corrected for the male and female population of the medical service of the Hospital during the period, 41.5 per cent were males and 58.4 per cent were females (82). The mortality statistics from the Bureau of Census of the U. S. A. for the period 1927 to 1932, a period when the criteria for the diagnosis of the disease were quite well-known, show a ratio of 47 males

to 53 females. The mortality from pernicious anemia in the group insured by the Metropolitan Life Insurance Company for the period of 1931 to 1935 was 10 per cent higher in females (1). Data collected by Cornell (78) from various countries other than the U.S.A prior to the introduction of liver therapy showed a mortality from the disease of 47.5 per cent in males and 52.5 per cent in females, which difference is analogous to that shown by the Bureau of Census statistics. But, with the data available it is not possible by a legitimate statistical inquiry to determine whether the increased incidence of achlorhydria in females correlates well with the increased incidence of pernicious anemia in females.

Thus, it appears that a decline or disappearance of the "intrinsic factor" may occur with advancing age; but whether the decline is due to ageing per se, or is related directly to achlorhydria or to gastritis and their causes is uncertain.

Gastric and duodenal ulcer, or "peptic ulcer"

The death rate from gastric ulcer (table 3) becomes progressively higher with advancing age up to 75 years in both males and females (1). By contrast the death rate from duodenal ulcer does not show much change beyond the 5th decade. This increase in death rate with advancing age can be accounted for mainly by the increased lethality of the major complications of ulcer disease, namely, hemorrhage and perforation (83). Not only is hemorrhage more lethal in older persons but it also occurs more frequently in them. Furthermore, the later in life an ulcer starts, the more likely it is to bleed (83). Gastric ulcer causes death more frequently than duodenal ulcer, although duodenal ulcer occurs clinically more frequently than gastric; this is chiefly because the perforation and hemorrhage in gastric ulcer are more serious than perforation and hemorrhage from duodenal ulcer, and because a duodenal ulcer is more likely to cause symptoms than a gastric ulcer (83). This is supported by the observation that as age advances the death rate from gastric ulcer increases more than the death rate from duodenal ulcer.

On the average, the age at onset of symptoms is higher for gastric than for duodenal ulcer; 19 per cent of patients with gastric ulcer have their first symptoms after the age of 50 whereas the corresponding figure for duodenal ulcer is 9 per cent (83). A number of authors (84, 85, 86, 87, 88, 89, 90) have recently called attention to the fact that the symptoms of peptic ulcer may appear for the first time in elderly individuals.

The postoperative jejunal ulcer is less likely to occur when a gastrojejunostomy is performed after the age of 50, a clinical impression widely accepted. The impression is supported by some statistical evidence (83), and is usually ascribed to the decline in gastric acidity that occurs with age.

Carcinoma of the stomach

Carcinoma of the stomach, like most other cancer, shows a strong tendency to increase in incidence with age (fig. 3). Because gastric cancer is

TABLE 3

Averages of annual death rates per 100,000 in whites

(Dublin and Lotka (1))

Age	Duodenal ulcer				Gastric ulcer			
	Males		*Females*		*Males*		*Females*	
	1931–1935	1921–1935	1931–1935	1921–1935	1931–1935	1911–1935	1931–1935	1911–1935
years								
20–24	0.8	0.7	0.2	0 2	1.0	1.7	0.6	1.1
25–34	2.8	2.4	0 2	0 4	4.1	4.4	0 9	1.7
35–44	5.5	5.1	0.9	0.9	11 8	10 7	1.7	3.0
45–54	8.5	7.0	1.2	1.3	21.4	16.8	3.7	4.7
55–64	10 9	7.9	1.9	1.8	25.4	18.8	5.3	7 1
65–74	9.9	7.6	2.1	1.6	26.0	20.8	8.0	12.4

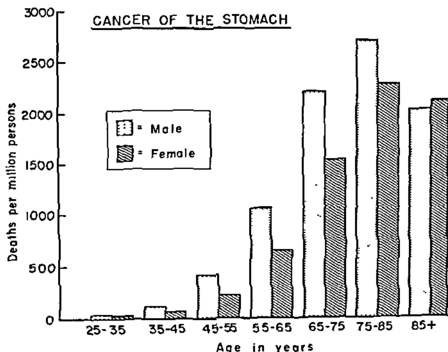


FIG. 3 The age incidence of gastric cancer. Data from Morris and Titmuss (91).

such an important cause of death and because the disease is usually relatively far advanced before it produces symptoms, much attention has been given to attempts to identify factors that might predispose to its development.

The question of transformation of gastric ulcer into gastric cancer has been debated extensively and there is still no general agreement concerning it. However, careful analysis of the clinical and histologic evidence indicates that the development of cancer from a benign ulcer of the stomach is, at most, an infrequent occurrence. Patients with proven gastric ulcer followed for a number of years do not develop gastric cancer any more frequently than persons without gastric ulcer (83).

The relationship of atrophic gastritis to gastric cancer has been widely considered. All observers agree that almost all stomachs with carcinoma show some atrophy of the uninvolved mucosa. However, there is little agreement on the character, distribution and severity of the gastritic changes in carcinomatous stomachs (34, 92, 93, 94).

The incidence of gastric atrophy is so high in normal persons above the age of 40 (see above) that its high incidence in cases of gastric cancer cannot be taken as an indication of a causal relation. On the other hand, the possibility of a causal relation cannot be dismissed, and, as Schindler (94) points out, the severity of the atrophy may be an important factor in determining its malignant propensity. Findley et al. (95) followed 100 patients with gastroscopically diagnosed atrophic gastritis, but without pernicious anemia, for an average period of 8.5 years. Two benign polyps, but no gastric cancers were observed to develop in these patients. More studies of this type are needed.

In patients with pernicious anemia the incidence of both benign polyps and gastric cancer is higher than in the general population (96, 97, 98, 99). The nature of this relation has not been determined and a number of theoretical possibilities exist. For example, the 2 diseases may be genetically associated, or the achlorhydria, the gastritis, or the gastric polyps may lead to gastric cancer, or the treatment with liver extracts may be a factor.

Benign gastric polyps, with or without pernicious anemia, are generally regarded as precursors of gastric cancer (100).

Patients with gastric cancer show a distinct tendency toward hypo- or achlorhydria. Here again the problem of which is cause and which effect, or if there is a cause-effect relation, remains unsettled. Theoretically, reduced acid secretion could predispose to or could be caused by gastric cancer, or they could both result from a common cause. Niazi and coworkers (101) have shown that achlorhydria occurs significantly more frequently in patients with gastric cancer than in patients with extragastric cancer; the latter group shows no higher incidence of achlorhydria

and hypochlorhydria than would be expected for their age group. State and co-workers (102) studied the secretory response to histamine in 3,416 persons over 50 years of age, and found achlorhydria in 15 per cent and hypochlorhydria in an additional 20 per cent. X-ray studies in these asymptomatic hypo- and achlorhydric persons revealed 10 gastric carcinomas and 28 benign polyps. The study by Comfort and Kelsey (103) is a remarkable one. In 277 cases of gastric cancer in which gastric analyses had been performed 2 or more years before the diagnosis of cancer was established, subnormal acidity was characteristic of these patients at all intervals up to 25 years before cancer was diagnosed. More studies of this type are needed because they suggest that gastric cancer develops relatively more frequently in persons with long standing subnormal acidity. It is interesting to note that duodenal ulcer patients, who as a group manifest higher than normal acid secretion, have a lower incidence of gastric cancer than the general population (83).

Gastric motor activity

THE POSITION AND PERISTALTIC ACTIVITY OF THE STOMACH. The position and shape of the stomach depend on the arrangement and development of the different muscular layers and their tone. Some believe that the relative amount of fat present in the abdomen, and the tone of the abdominal musculature are also concerned; such a view has been questioned, however (46, 104, 105, 106).

The shape of *the filled infant's stomach* is, like that of the adult's, not fixed. It may manifest the form of a flask lying on its side, or it may be oval or globular (4). It is more frequently located horizontally and obliquely than vertically. The more vertical position, or J-shape, characteristic of many children and most adults first appears about the age of 3 years.

Peristalses are difficult to observe in the infant's stomach because the waves are not as deep as those which occur later. The peristaltic mechanism is present at or soon after birth because in the presence of hypertrophic pyloric stenosis, which may become manifest a few weeks after birth, visible peristalses are evident on inspection of the abdominal wall (107). Active peristalses are evident at 3 months (108).

Wright (46) has studied carefully the position and shape of the *stomach of healthy children* (243 subjects) ranging from 6 to 15 years. He found the shape and position to vary widely, but the variation became greater with the approach of puberty. The J-shaped stomach became the characteristic type at 12 years of age The position of the stomach was the same in males and females up to the age of 11, after which the females manifested a tendency to have lower stomachs. Moody (105) found the stomach to be higher in British boys 7 to 14 years of age than in men of medical school

age. The foregoing observations and those of others show that "gastroptosis" and "gastric atony" are rare in children (109), and that the shape and position of the stomach changes with age. The change to the characteristic adult type begins at the age of 3 and becomes definite after the age of 11, when the first evidence of a sex difference appears.

The position and shape of the stomach have been studied in 600 *young adults* of university age, equally distributed between the sexes, by Moody, Van Nuys, and Chamberlain (106). The J-shaped stomach, reaching from 3 to 7 cm. below the interiliac line, was found in 80.6 per cent of the subjects. The average position of the greater curvature was 2.5 cm. and 4.5 cm. below the interiliac line in men and women respectively. In 25.6 per cent of the men and 13 per cent of the women the greater curvature was above the line. The hypertonic stomach (high, short and obliquely situated) was present in 17.1 per cent of men and 7.1 per cent of women; the hypotonic stomach (long, markedly hooked) was present in 3.6 per cent of men and 15 per cent of women; the orthotonic stomach or the stomach of average length was present in the remainder. The hypersthenic person (broad and short thorax, wide intercostal angle, abdomen broad and large) tends to have a high-lying stomach and the asthenic person a low-lying stomach. For example, the fact that in 44 per cent of British and only 22.5 per cent of American young adults studied, the stomach was 2 inches below the interiliac line was found to be due to the difference in the body habitus; the British young adults had narrower chests and smaller intercostal angles (105). However, no constant relationship exists between the strength and build of a person and the shape and position of the stomach.

Data similar to the foregoing are not available for various decades after thirty. A start has been made by Moody (105) who studied the radiographs of 100 British patients, 50 males and 50 females, with gastrointestinal complaints. The ages of the patients ranged from 40 to 81 years. It was found that low stomachs occur more frequently in healthy young British adults than in elderly British patients with gastrointestinal complaints.

An investigation of the change of the shape and position of the stomach in subjects above the age of 30 and devoid of gastrointestinal complaints should throw some light on the relation of age to the gastric motor mechanism. But, since the shape and position of the stomach is not always related to the rate of gastric evacuation, actual studies of the rate of evacuation at different ages are necessary.

THE MOTILITY OF THE EMPTY STOMACH. HUNGER MOTILITY. The studies of Carlson (110) and his students have shown that the stomach of the human infant manifests greater hunger motility than the stomach of the adult. In the breast-fed infant, the first period of hunger motility starts 2.5 hours (average) after a meal; in the young adult from 4 to 6 hours after

the meal. The periods of hunger motility occur more frequently in the infant. In the infant the quiescent periods range from 10 to 60 minutes in length; in the adult from 1 to 3 hours. A study of the hunger motility of the human stomach by decades has not been made

A study has been made of the hunger motility of the stomach of dogs at different ages (110). The most constant difference occurs in the length of the periods of quiescence and activity. The periods of quiescence are shorter, and the periods of hunger activity are longer in young than in old dogs. Old dogs must also be fasted longer than young adult dogs before hunger contractions appear (111).

The decrease in the hunger motility of the stomach with age may be due to two factors, namely, (a) the age of the musculature or the motor mechanism of the stomach, and (b) the decline in metabolism which may reduce the quantity of the blood-borne, chemical stimuli of the hunger mechanism. The latter is not primarily concerned because Patterson (112, 113) found that prolonged fasting, though it increased the hunger contractions some, did not lead to contractions which approached those of young dogs in vigor. Thus, it appears that the irritability of the gastric motor mechanism concerned in hunger contractions decreases with age. To what extent the extrinsic nerves of the stomach may be concerned in the decrease in hunger motility with age has not been determined.

In acute gastritis the stomach is relatively atonic and hunger contractions do not occur (110, 114).

The rate of gastric evacuation

It has been indicated above that the motility, and proably the tone, of the stomach is greater in the infant and child than in the adult. It is well established that increased motility and tone of the stomach and increased hunger, under normal conditions, cause the stomach to empty more rapidly. Thus, a relatively more rapid rate of gastric evacuation should be expected to occur in the infant and child than in the adult. But, since the quantity and quality of food also influence the rate of gastric evacuation, and since many different kinds of test meals have been employed, it is impossible to compare much of the data reported in the literature. The x-ray method gives reliable results only when the same technique is employed; even then, a single examination is not very reliable. A single examination would be indicative if performed in a large number of subjects; but at present there are no data in the literature which establish the rate of gastric evacuation in the various decades of life. Certain comparisons, however, may be made.

It is generally agreed that the infant's stomach will evacuate 100 or 150 cc. of milk in from 1.5 to 3 hours, occasionally more rapidly (115). In

young adults 400 cc. of milk is evacuated in from two to three hours. The same is true of the various types of barium meals used by roentgenologists, the maximum limit of normal in the adult being from five to six hours. Some roentgenologists have the impression that the stomach of persons over the age of 65, not complaining of dyspeptic symptoms, empties more slowly than the stomach of the young adult, but definite proof is not available. *It is generally thought that the J-shaped or long stomach empties* more slowly than the steer-horn or short stomach; but there is no proof. Both types of stomach may be associated with dyspeptic symptoms, the short stomach when it is hypermotile and the long stomach when it is atonic and hypomotile. Of course, both types of stomach exist normally without producing symptoms.

Since gastric acidity declines and the incidence of achlorhydria increases after the age of 45 years, these factors may affect the rate of gastric evacuation. It is generally considered that in the presence of achlorhydria the stomach empties faster; but, this cannot be considered as established on the basis of the data presented in the literature. The data of Vanzant and her collaborators (51, 52) show that with advancing age less contents are aspirated after the Ewald meal. Dedichen (117) who studied the stomach of 99 healthy old people from 67 to 92 years of age by the Ewald method and found the incidence of achlorhydria to be 66 per cent, states that the stomach of the aged empties more rapidly than that of the young adult. It is also claimed that the stomach of patients with pernicious anemia who have achlorhydria, empties faster than normal (79). However, Keefer and Bloomfield (118) do not report a high incidence of rapid gastric evacuation in the achlorhydric patients they studied, and Jacobson and Palmer (119), using the barium meal method, could find no evidence of more rapid than normal emptying in patients with pernicious anemia. Davies and James (75) who present data obtained on 100 patients ranging from 65 to 90 years by the use of an Ewald-gruel meal, find that the stomach of elderly achlorhydric subjects empties faster than that of non-achlorhydric subjects. Van Liere and Northup (118a) found no difference between the rate of evacuation of a "gruel" meal in 12 old persons who were able to do light work and 49 medical students. The clinical impressions of numerous authors (55, 120), might be quoted, but the data available are inadequate to warrant compilation and definite conclusions. Even the extensive data of Vanzant (51, 52) referred to above, are not clearly interpretable because the reduction of the amount of gastric contents with advancing age may be due either to decreased secretion of acid or to more rapid emptying, or both. This criticism applies to all of the studies in which gastric emptying was studied by means of a secretory test meal.

It is of interest that 100 cc. of milk is evacuated from the infant's stom-

ach at about the same rate that 400 cc. is evacuated from the adult's stomach. This may be related to two differences which exist between the stomach of the infant and that of the adult. The mean acidity of the adult's stomach is four times that of the infant (58) and the "capacity" and weight of the adult's stomach at 20 years of age is approximately four times that of the infants at the age of 1 year (27).

Dyspepsia among men and women above 40

According to a report from the Mayo Clinic (12) dyspepsia or "indigestion" is among the complaints of almost one-half of patients between thirty and sixty years of age. This evidence shows that symptoms referable to the digestive system are among the most common of all complaints, a fact that is generally accepted. This is because disorders of organs outside the digestive system may cause functional disorders of the alimentary tract either by causing changes in the composition of the blood or by disturbing the activities of the tract reflexly through the nervous system.

In males aged forty and above who complain primarily of dyspepsia, peptic ulcer ranked first as the cause; in women gallbladder disease ranked first. In 17 per cent of the males and 5.8 per cent of the females cancer of the organs of the digestive system, chiefly the stomach, was the cause of the dyspepsia. In 49 per cent of the men and 38 per cent of the women in whom dyspepsia was the primary complaint, the dyspepsia was due to some disorder of the digestive organs that demanded careful diagnosis and early medical or surgical attention (fig. 4).

These observations show that the medical profession has the responsibility of educating laymen concerning the dangers of using therapeutic nostrums for dyspeptic symptoms and the responsibility of making an accurate diagnosis of the cause of dyspeptic symptoms particularly in persons above the age of 40 (121).

Pancreas

Growth and senescence of the pancreas as indicated by the post-mortem weight of the organ

The growth of the pancreas of the rat has been carefully studied (3). Histologically the human pancreas at birth, like the salivary glands, is relatively deficient in parenchymatous tissue. Secretory granules are present after the sixth fetal month and evidences of secretion appear in the gland at this time (4). Scammon (4, 122) finds the average weight of the pancreas of the newborn human to be 3.54 grams. The data indicate that the weight of the pancreas decreases after the age of sixty. The effect of inanition, which probably existed in Boyd's (28) subjects prior to death, on the acinar and islet cells of the pancreas is uncertain because of con-

tradictory reports (123). Wet weights, especially without histological study, yield unreliable data. As in the case of the gastric mucosa and salivary glands, statements are found to the effect that the pancreas in old persons is atrophic, but the evidence is not convincing. Goodpasture (6) in his study of fifty old dogs found degenerative changes in the pancreas. Grossly its lobulations were more distinct and its consistency was firmer than in the younger adult. In an important study of the histologic changes in the

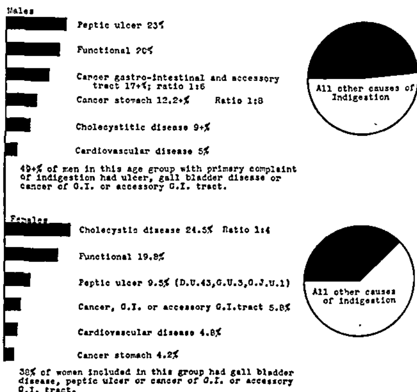


FIG. 4. The most frequent causes of dyspepsia among men and women aged 40 and over (Rivers, 121).

pancreas associated with ageing Andrew (124) has shown that a similar sequence of alterations occurs in the rat and in man. Proliferation of cells of the interlobular and intralobular (intercalated) ducts, often in the form of apparently solid masses of cells, was followed by lumen formation and expansion. This led to flattening of the epithelium and locule formation. Where the locules were multiple, their walls ruptured, forming large, irregular cavities. Some locules contained a material which resembled keratin. Andrew considered the metaplasia in the interlobular ducts to be a manifestation of a general tendency of the duct epithelium to proliferate and become squamous in senile individuals. Adipose tissue invasion also oc-

curred. Degenerative changes in acinar cells were also seen, including loss of basophilia of the cytoplasm and hypertrophy or atrophy of nuclei. This series of changes were present in a moderate to marked degree in all of 25 human subjects 70 to 90 years of age Wallace and Ashworth (125) describe similar changes in the pancreas of aged humans

External secretion of the pancreas

The effect of the hormone secretin on the secretion of the pancreas of the newborn animal has not been adequately studied. Neither has the effect of ageing on the external secretion of the pancreas in animals been studied. If degeneration of the external secretory cells or the acinar cells of the pancreas occurs in the aged, less pancreatic secretion will be formed This is based on the fact that the response of the pancreas to the hormone secretin is related to the amount of acinar tissue (126). Furthermore, functional regeneration of acinar tissue apparently does not occur in the dog. (Functional regeneration does occur in the stomach and liver) Whether the pancreas of man manifests functional regeneration is not known. If all the acinar tissue is destroyed, it is known that appreciable steatorrhea (fat in the feces), creatorrhea (meat fibers) and sometime amylorrhea (starch) occur. But, we do not know the amount of acinar tissue that must be destroyed to cause the first detectable evidences of incomplete pancreatic digestion (127). Helmer, Fouts, and Zerfas (128) have found that patients with pernicious anemia who show involvement of the central nervous system have decreased tryptic activity in the duodenal contents. Johnson and Davis (134) reported that 21 of 35 cases of pancreatitis which they studied were in persons over age 45.

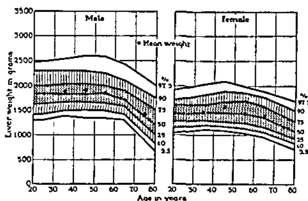
Studies on pancreatic enzymes in duodenal fluid have shown that the starch digesting power is feeble under one year, after which it is plentiful. The fat digesting or lipolytic power is also feeble under one year and does not reach the adult range until about the twelfth year. The proteolytic or protein digesting power is plentiful throughout infancy and childhood (47, 129, 130, 131). The data provided by Meyer and his associates (19, 20) show that in the aged the amylolytic and lipolytic activity of the fasting duodenal contents is only slightly diminished, whereas the proteolytic activity is decidedly decreased. After stimulation with oleic acid the volume, bicarbonate, amylase and trypsin of the duodenal contents of old persons were not diminished as compared with young persons, but the lipase was depressed by about 20 per cent (24). A decrease of this magnitude is unlikely to produce digestive impairment (132). Diastase in blood serum shows no fall in older people but lipase does decrease (138).

It is reported that as age advances the vitamin C content of the pancreatic tissue decreases (133).

Liver

Growth and senescence of the liver as indicated by postmortem weight of the organ

The growth of the liver of the rat has been studied carefully (3). The human liver grows quite steadily up to the age of 20 (27, 135). The average weight of the human liver at birth is 135 grams. Its weight is more than doubled the first year, and tripled in the third. By puberty the liver weighs about 10 times its natal weight. After the age of 20 the weight of the liver remains fairly constant in both males and females. Data on liver weight have been compiled by Edith Boyd (136), and are the best available (fig.



5). They were obtained from cases of death from accident, and the factors of disease and inanition, which markedly affect the weight of the liver, were controlled.

Frischmann (137) has reported the results of an histologic study of the effect of ageing on the connective tissue stroma of the liver in man. He concludes that the increase in connective tissue previously reported to occur in the liver of the aged is due to pathological processes and not to physiological senescence. He failed to find an increase in the connective tissue in Glisson's capsule and in the reticular lattice work of the liver in ten cases ranging in age from 60 to 86 years of age. Andrew (139) in a correlated study of the mouse liver and the human liver confirmed this absence of change in the amount or character of connective tissue with ageing. He did, however, find in both species giant nuclei and multiple nucleoli occurring with increasing frequency as age advanced.

Changes in functional activity and resistance to hepatotoxins with age

Since the factor of safety of the liver is large, the decrease in the weight of the liver with age should not, of itself, cause any evidences of hepatic insufficiency (140). In an adult dog four-fifths of the liver may be removed without evidences of hepatic hypofunction by the ordinary tests of liver function. Unless ageing *per se* affects the functional activity of the liver to a greater extent than its weight, evidences of hypofunctioning of the liver should not become manifest with ageing. Further, in the adult it is known that the regenerative capacity of the liver is remarkable. After the surgical removal of 70 per cent of the liver, the weight and volume of the liver returns to about 75 per cent of the original within a few weeks. After central necrosis of the liver induced by chloroform, complete recovery occurs in a few days (141). After exposure to various hepatotoxins the liver shows marked recovery and the regenerated cells manifest an increased resistance to these poisons (142). Regeneration of liver cells occurs only when the blood supply is normal and the bile ducts are not obstructed (140).

The relative ability of the liver to regenerate after the surgical removal of a portion has not been determined in old animals. The resistance of the senile liver of dogs to chloroform poisoning has been studied by MacNider (142, 143). In 22 dogs ranging in age from 8 to 15 years, which had been kept under laboratory conditions for long periods, the liver manifested histologically a diffuse atypical epithelium much like that found in the liver of a young adult following the repair which occurs after uranium nitrate or chloroform poisoning. The liver cells and cords were flattened and stained intensely as though the cytoplasm was condensed; the nuclei were relatively enlarged and hyperchromic. In addition incompletely undifferentiated cells formed syncytical structures. Atypical epithelium has also been described in the liver of old dogs by Goodpasture (6). He has described the changes in much detail; they are characterized chiefly by degeneration which is associated with simplification of structure and regressive alterations with a tendency in some areas to manifest cellular overgrowth. The most characteristic degenerative change found was the presence of crystals in the nuclei which are insoluble in acids and soluble in strong sodium hydroxide. Similar crystals were found in the liver of old dogs by Brandts (144).

In 13 of the 18 old animals subjected to experimentation by MacNider (143), the liver reacted normally to the phenoltetrachlorphthalein clearance test. The liver of every animal manifested greater tolerance to chloroform than the liver of young adult dogs. Thus, dogs in ageing may naturally acquire an atypical hepatic epithelium similar to that which occurs as a

repair process following liver injury induced experimentally with an hepatotoxic agent. Rafsky and Newman (145) performed liver function tests on 42 subjects 65 to 86 years of age. They reported abnormality in hippuric acid synthesis in 70 per cent, in cephalin-cholesterol flocculation in 76 per cent and in percentage of free cholesterol in 71 per cent. However, they did not apply their test procedures to a control group of young persons. Further studies on liver function in aged persons are needed.

Studies of the bile volume output and the composition of the bile in the aged have not been made. Warthin (5) states that hyperbilirubinemia occurs in the aged, but the statement is not supported by evidence. The results of such studies would have to be interpreted in the light of studies on the histology of the liver to render them truly significant in so far as ageing *per se* is concerned because cirrhosis of the liver interferes with hepatic function and this disease markedly increases in incidence with advancing years (1).

The vitamin C content of the liver, like the pancreas, apparently decreases with age (133). Some meager and poorly controlled observations indicate that the vitamin A content of the liver increases shortly after birth in dogs and humans (146).

The effect of ageing on the glycogen content of the liver has been studied in the rat (147). The content of liver glycogen increases after birth up to 40 days of age when it exceeds 8 per cent. It then decreases slowly to 4 per cent at the age of 75 days. In rats from 19 to 24 months old the liver glycogen is approximately 4 per cent.

Gallbladder

Growth

The gallbladder of the newborn infant is relatively small. During the first two years of life its capacity increases so that by the end of the second year, the ratio of "the capacity of the gallbladder to liver weight" is the same as in the adult (4). According to Gundobin (148), the contents of the gallbladder at autopsy in infants from 1 to 3 months of age averages 3.2 cc. and from 1 to 3 years of age, 8.5 cc. of bile. The functional capacities of the gallbladder at different ages are best determined by the method of cholecystography and the data which have been so obtained will be given later.

Functional activities

The activities of the gallbladder concerning which most is known, are concentration of the hepatic bile and evacuation (127). The normal gallbladder concentrates the hepatic bile which enters it from 4 to 10 times; under conditions of stasis, 20 times. The gallbladder evacuates most of its contents after a meal containing fat, protein, or acids such as are found

in gastric juice, vinegar and fruits. No facts are available regarding the capacity of the gallbladder to concentrate at different ages, although the effects of disease on its capacity to concentrate are known. More is known concerning the relation of age and sex to the rate of evacuation of the gallbladder.

The best data on the relation of age and sex to the rate of evacuation of the gallbladder have been provided by Boyden and Granthan (149). Eighty-four subjects were used, ranging from 6 to 78 years of age. In childhood the rate of evacuation was found to be faster than in early maturity, the difference being due to a faster rate in boys than in girls. After puberty the male gallbladder emptied more slowly than the female. The gallbladder of elderly women emptied faster than that of elderly men. Thus, it appears that the gallbladder of the female empties at a rather constant rate from childhood to old age, and at the onset of puberty some influence operates in the male to slow down the rate so that from puberty on, the gallbladder of the male empties more slowly than that of the female.

Since gallbladder disease increases definitely with age and in chronic cholecystitis the gallbladder cannot be visualized, Boyden's group of elderly persons represents those subjects whose gallbladder had escaped pathological alteration. This fact obviously increases the value of the data in so far as the effect of ageing per se on the gallbladder is concerned, and indicates that the power of evacuation does not lessen with age per se.

In regard to the size of the gallbladder, the data of Boyden and Granthan (149) show that it is not significantly related to the rate of evacuation. This is important because the mean cholecystographic volume of the elderly women was 29.0 cc., of the elderly men 33.4 cc., of the young women 24 cc., of the young men 30.8 cc., of the girls 13.5 cc., and of the boys 13.9 cc. In a personal communication, Boyden gives an average volume of 30.3 cc. for the gallbladder of 32 young men, average age 25.7 years, and of 30.6 cc. for 36 older men, average age, 60.1 years. Regardless of the differences in size, the mean differences between the rate of emptying of the gallbladder in childhood and old persons are not significant, and the gallbladder of the young adult empties slower than that of both of the other groups.

So, it would appear as if the gallbladder of the old person returns to that of the child in regard to rate of emptying. It would be necessary to have data on a larger number of children and old people before such an observation could be considered to be a fact. Yet, it is clear that if the gallbladder of old persons escapes disease, it will evacuate well. It may be that the gallbladder which empties well throughout life is the one more likely to escape disease.

If it be true that the gallbladder of old persons evacuates as rapidly as

that of a child, and more rapidly than that of a young adult, it follows that the gallbladder of the old persons should either manifest hypertrophy of the musculature, or the resistance offered to the flow of bile from the common duct into the duodenum should be less than in the young adult. (Of course, the gallbladder of the young adult may be more subject to reflex or hormonal inhibitory effects.) No evidence is available concerning the latter possibility, and the evidence concerning the former is contradictory. Lütkens (150) could not substantiate Charcot's belief that the musculature of the gallbladder is atrophied in the old person. In fact, he gained the impression that the gallbladder of old persons manifested *some hypertrophy of the entire wall with some sagging. He thought the* sagging might be due to weakening of elastic fibers. In some instances sclerosis of the blood vessels and atrophy of the mucosa of the gallbladder may be found in old persons, but its effect on gallbladder function was not determined. In fifty old stray dogs, Goodpasture (6) found the mucosa of the gallbladder to be thickened and to manifest a polypoid overgrowth with dilated glandular crypts filled with a substance staining like mucus. The rate of emptying and the concentrating ability of the gallbladder of old dogs has not been studied.

It would appear from the evidence now available that the greater susceptibility of the female gallbladder to disease is due to metabolic disturbances which alter the composition of the bile, or to infection, or to stasis resulting from disturbance of the sphincter of Oddi mechanism, rather than to motor insufficiency of the gallbladder. This is because the gallbladder of the non-pregnant adult female tends to empty faster than that of the adult male. Considerable evidence exists (127) showing that the gallbladder of pregnant women empties more slowly than normally and tends to be distended (151). Gerdes and Boyden (152) have shown quite definitely that during pregnancy the gallbladder does not empty as rapidly or as completely as before or as in nulligravidae. The cause or causes of gallbladder retention in pregnancy is not known, but Westphal (153) has performed certain experiments, the results of which indicate that a hypertonus of the sphincter of Oddi exists during pregnancy. The gallbladder of the pregnant guinea pig is refractory to the evacuating effect of the hormone cholecystokinin; the female sex hormone is only partially concerned (154). This is a field of investigation that deserves more attention than it has received because of the high incidence of cholecystopathy, including cancer of the organ, in women who have borne children.

Gall stones

Although it is well known that gall stones may occur in children, all observers agree that less than one per cent of the cases of cholelithiasis

occur in persons under 20 years of age. The incidence of gall stones increases with each decade above 20, and becomes marked above the age of 40 (156, 157). This is illustrated by the data in table 4; the data are based on

TABLE 4

Biliary calculi

Averages of annual death rates per 100,000 (Dublin and Lotka)			Data from 2,621 consecutive autopsies, Cook County Hospital, Chicago, 208 cases of gallstones, 1929–1932 (Jaffe†)		
Age periods	Males, 1911–1935	Females, 1911–1935	Age periods	Males	Females
		Whites			
years			*years*	*per cent*	*per cent*
1–74*	1.4	4 9	Average incidence	6 76	17 57
45–74*	5.8	19 3			
20–24	0.1	0.5	21–30	0	5
25–34	0.4	2.3	31–40	1.45	11.51
35–44	1.4	5.9	41–50	4 24	21 90
45–54	3 5	13 3	51–60	6 75	17 07
55–64	6.5	22 4	61–70	11.20	29.03
65–74	10 6	30.0	Above 70	13 90	24 44
		Colored			
1–74*	0 7	1.9	Average incidence	1.04	10.23
45–74*		6.8			
	2 6				
20–24	0 3	0.5	21–30	0	3.28
25–34	0 5	1.4	31–40	0.73	7.50
35–44	0 8	2 8	41–50	0	12 24
45–54	1 8	5.1	51–60	1.86	16.27
55–64	3 0	7 2	61–70	4.34	25.0
65–74	3 9	10 6	Above 70	6.66	20 0

* Standardized for age—Dublin and Lotka (1).

† Jaffe (155). The deaths in this series were, of course, not necessarily due to gallstones. The number of cases of gallbladder disease in relation to the number examined in each age and sex group are considered by the author. Among the colored persons the pigment variety of stone predominated; among the white the mixed variety predominated.

mortality and autopsy statistics because these are the most reliable. There is a marked variation in the statistics on different countries and races (155), but the increase with age holds true. The increased incidence of gall stones in the female is seen in most occidental peoples, but in Japan, for example, where the pigment type of stone predominates, a sex dif-

ference does not seem to exist. The observation that cholelithiasis is more common in whites than in negroes is truer of the males than the females (table 4).

The clinical evidence (158, 159, 160, 161) indicates that all types of cholecystopathy increase with advancing age. The exact incidence with each decade is uncertain.

Small Intestine

Growth and senescence

The growth of the small intestine has been studied in the rat (3); the effect of senescence has not been studied. The growth of the small intestine of the human fetus has been studied by Scammon and Kittelson (162). At birth the small intestine of the human infant measures about 340 cm. in length; its length is doubled by the age of puberty, and in the adult (14 cases only) its average length is about 760 cm. The data given by Vierordt (163) indicate that the weight of the human intestine increases up to the age of 42, after which it decreases. The data are so meager that it cannot be concluded that the weight of the intestine in the aged is less than that of the mature adult. The same uncertainty exists in regard to the effect of age on the length of the small intestine. It is generally stated and believed, however, that the intestine of old persons manifests atrophy of the mucosa and musculature. Inanition in rats results in an increase in the weight of the intestine due to edema and an atrophy of the cells of the mucosa (20); the same is true of human infants (123). It would appear, then, that reliable data regarding the effect of ageing on the weight and histology of the intestine could be obtained only from persons dying from some sudden cause.

Functional activities

Few data are available on the rate of passage of inert materials through the small intestine in the young and mature adult; none are available for infants and children, and none for the aged. The secretion of succus entericus and the rate of absorption of food from the small intestine in old animals have not been studied. Takashina (164) presents some evidence indicating that adrenaline is absorbed more rapidly from the intestine of the infant and child than of the adult, but the significance of his observations is questionable.

Only a few studies have been done on intestinal absorption in aged human subjects. Horvath et al. (167) found no definite evidence of abnormality in the oral glucose tolerance test in aged men but Meyer et al. (168) found that in the galactose tolerance test the height of the peak blood level was lower in old individuals. Kountz and coworkers (169) found

that 11 out of 27 old people were in negative nitrogen balance but the average daily output of nitrogen in the feces was not increased above accepted normal values (170). The absorption of vitamin A and carotene is not impaired in the aged (171, 172). Using the chylomicron counting technique, Becker and coworkers (173) found a higher peak and a marked delay in return to basal levels which they interpreted as being due to impaired fat absorption. In a similar study by White and coworkers (174) the elevated and prolonged chylomicron counts were correlated with inactivity but not with age.

Except for early childhood (1 to 4 years), death from intestinal obstruction is chiefly a condition of advanced age (above 50 or 55 years). This fact does not necessarily indicate the existence of some weakness of the intestine in elderly persons. This is true for two reasons. (a) The incidence of hernia markedly increases above the age of 55, and, although hernia is more likely to become strangulated during the period of active adult life, it is the most common cause of intestinal obstruction. (b) Abdominal adhesions are the second most frequent cause of intestinal obstruction and these occur most frequently as an early or a late result of operations on the appendix and pelvic organs. Abdominal and pelvic operations have increased in recent years. Operations on the appendix are frequent at all decades and operation on the pelvic organs are most frequently performed on mature or elderly adults These facts explain the increase in deaths from intestinal obstruction observed during recent years. Neoplasms of the colon rank third as a cause of intestinal obstruction and, of course, occur more frequently with advancing years (1, 165, 166).

Appendix

Growth and senescence

Although the growth of the appendix in the human fetus has been studied, relatively little is known concerning the effect of age on the organ, when the frequency of disease in it is considered. In infancy and childhood it contains a relatively large amount of lymphoid tissue, which resembles that of the tonsil. Although a considerable amount of lymphoid tissue is present in the appendix at birth, the amount increases during the first year as it does in other portions of the intestinal tract. The amount of elastic tissue in the appendix and intestine increases greatly during the first year (4).

The appendix in the newborn infant is usually connected to the cecum by an enlarged base, the conus appendicis, i.e., in the infant the cecum frequently tapers into the appendix without there being a clear line of demarcation. The appendix measures from 2 to 6 mm. in diameter, and from 2 to 8 cm. in length at birth. It usually increases rapidly in length

during the first year, usually reaching a length of from 8 to 10 cm. and becomes a more discrete organ. After the first year its growth is very slow and irregular (4). Its content of lymphoid tissue is said to diminish with age as is generally true of lymphoid tissue throughout the body and in the alimentary tract. The appendix possesses a lumen extending to its tip in all infants and children. According to Ribbert (175), the lumen shows a tendency to undergo obliteration as age advances. This obliteration starts at the tip and gradually extends toward the cecal end or base of the appendix. In 25 per cent of 400 cases the lumen was more or less obliterated; in adults over 50, it was obliterated in one-half of the cases. This is said *to occur in the absence of the evidences of existing or previous inflammation*, and to be a true process of involution associated with ageing. However, this is uncertain.

Appendicitis

The great immunity of the nursing infant to appendicitis has been attributed to diet and also to the anatomy of the appendix; the cecal end of the appendix is more patent in the infant. In the infant, the wall of the appendix is relatively thin due to the slight development of the mucosa and lymphoid tissue (67, 176, 177). The alleged relative infrequency of appendicitis in the latter years of life has been attributed to obliteration of the lumen and a diminution of lymphoid tissue. The mortality rate from appendicitis is apparently quite uniform from the decades above the third (1). The disease in the aged is regarded as peculiar or atypical in type and as having a higher mortality (178). This is attributed by Maes (179): (a) to the atrophy of the protective lymphoid tissue, predisposing to rapid gangrene and to a more rapid spread of the infection to veins and surrounding tissue, and (b) to the "naturally lowered resistance of elderly patients".

The clinical experience that the incidence of appendicitis is higher in males (about 25 per cent) than females, is confirmed by the mortality rates (1).

Colon

Growth and senescence

The growth of the large intestine in the human fetus and in infants has been studied rather thoroughly (4, 162). At birth the large intestine weighs [illegible] 16 grams and is 65 cm. in length. At 3 years it weighs ap- [illegible] adult it weighs about [illegible] the pelvic or sigmoid portion of the colon is relatively greater in the fetus and infant than in the adult. This is also true of the rectum. The sacculations and the three

longitudinal bands (tenia) of muscle, so evident in the adult colon, are not very evident in the newborn, and develop during the first six months. The sacculated cecum typical of the adult does not appear until the third or fourth year. Although it is frequently stated that the colon atrophies and its musculature becomes thin and atonic with age, real evidence supporting the view is wanting (163).

Carcinoma of the colon has, in recent years, become as frequent as carcinoma of the stomach (210).

The activities of the colon

The activities of the colon are absorption, secretion and motility. The colon by absorbing water and inorganic salts concentrates the material entering from the ileum. Relatively little food material, other than water and salts, is absorbed from the colon of the dog and man, although some glucose and other soluble substances may be absorbed to a variable and a rather insignificant extent. Drugs are sometimes administered per rectum. The colon secretes mucus which serves to protect the mucosa and to lubricate the feces. At times the secretion of mucus may become excessive, a condition called mucous colitis. The motor activity of the colon serves to accomplish the condensation of the fecal mass, to move the feces downward and to effect defecation.

There is no evidence indicating that the absorptive and secreting capacity of the colon is decreased in old persons. It is claimed by some that one of the causes of constipation in the aged is a decreased secretion of mucus. This claim is not supported by actual evidence. The claim that the colonic musculature becomes atonic with advancing years has not been established by actual studies on the time of passage of marked contents through the colon or by barium enemata.

The effect of ageing on the musculature of the colon. Diverticulosis

Perhaps the best evidence regarding the thinning of the colonic musculature of man with advancing age is afforded by the increased incidence of diverticulosis of the colon with age. That the incidence of this condition increases with age is agreed to by all authors; further, this condition is said to be the most common pathological lesion of the colon seen by the surgeon and roentgenologist. When the diverticula become infected (diverticulitis), the condition is quite serious; when not infected, they may contain fecoliths. Diverticulosis is rare below the age of 35. The majority of cases are seen clinically by the physician in the sixth and seventh decades. But in the clinical reports which are reviewed up to 1935 by Lunding (180), the incidence in relation to the number of patients in each decade examined by the physician is not considered. Fifield (181), who examined

the colon in 10,167 consecutive autopsies, found that most of the cases occur between the age of 60 to 90; unfortunately he does not give the percentages in regard to age and sex in relation to the number of cases of each sex and decade examined. Kocour (182), who studied the incidence of the condition in 7,000 consecutive autopsies, gives the percentage of diverticula in relation to the number of autopsies performed in each age

TABLE 5

Age incidence of diverticulosis of the colon

From a study of 7,000 consecutive autopsies (Kocour, 182)

Age	Autopsis		White male	White female	Colored male	Colored female	Total
years							
21–30	566	Number	0	2	0	2	4
		Per cent*	0	1.9	0	1.19	0.7
31–40	895	Number	0	2	1	0	3
		Per cent	0	1.0	0.45	0	0.34
41–50	1,178	Number	4	3	5	3	15
		Per cent	0.8	1.5	1.9	1.6	1.27
51–60	1,024	Number	10	5	5	3	23
		Per cent	1.9	2.8	2.5	3.0	2.24
61–70	711	Number	28	9	4	5	46
		Per cent	6.4	6.9	4.4	9.3	6.47
70 up	137	Number	18	16	1	1	36
		Per cent	7.1	15.2	2.0	3.0	8.2

* The figures give the percentage of diverticula in relation to the number of necropsies performed in each case. Number of cases above 20 years of age examined total 4,811. The remainder under the age of 21 amounted to 2,189 and in this group no cases of diverticulosis were found.

decade. His data (table 5) show that the condition increases markedly after the age of 40, and beomes relatively stationary in the seventh and eighth decades. Telling and Grunner (182a) arrive at a similar conclusion when the clinical incidence observed by them is corrected to show the rate of occurrence of diverticulosis in relation to the population surviving at the various ages. Their estimates indicate a decreased incidence above the age of 75, which may be due to the mortality incident to infection of the diverticula. It is of interest that Kocour found the incidence of lesions of the gallbladder in persons above 40 years of age to be doubled in those having diverticula.

The most widely held theory of the cause of diverticulosis is that it is due to pressure from gas in the colon associated with weakness of the elastic or muscular tissue. This is supported by the report of Hausemann (183) that diverticula may be produced experimentally by distending at autopsy the colon of senile but not of young persons, with water under pressure, and by the observation that in a number of cases the diverticula are very numerous above a stricture of the colon. Constipation or colon stasis is considered to be a factor by some In this regard constipation is generally considered to be more frequent in women than in men, but a summary of the clinical cases of diverticulosis reported in the literature shows a frequency of 64.9 per cent in the male. Since many of the cases of diverticulosis are symptomless, it would appear that data from consecutive necropsies in which special attention is given to the condition would be more reliable. The data provided by Kocour (182) which is the largest series of necropsies performed in which data on the true percentage incidence is given, show that diverticulosis was about 33 per cent more frequent in the female. Although diverticula may be found throughout the colon, excluding the rectum where they rarely occur perhaps because the musculature of the rectum is more plentiful and uniformly distributed than in the colon, they are usually more frequent in the sigmoid than in the remainder of the colon. It is of interest in this connection that Kantor (184, 185, 186, 187) who has studied his cases of constipation in relation to the form, position and abnormalities of the colon, has found that the cause of most of the varieties of constipation lies in the distal colon. For example, redundancy of the sigmoid was one and one-half times more frequent in patients complaining of constipation.

No attempt has been made to produce diverticulosis experimentally in such animals as the pig and monkey, which have a colon like that of man. However, diverticula of the colon occur spontaneously in senile rats and the incidence of the condition is correlated with the diet. A diet lacking in a suitable kind and amount of roughage was found to predispose to diverticulum formation (188).

Gastrointestinal passage time

The average gastrointestinal passage time in breast-fed "normal" infants is about 15 hours; it varies from 4 to 28 hours. The time is usually longer in bottle-fed infants because cow's milk tends to constipate (107). The gastrointestinal passage time varies widely in normal adults. The time of appearance of an orally ingested test material in the feces varies in most adult subjects from 20 to 72 hours; the time of final appearance varies from 2 to 7 days (189, 190, 191). Similar data for elderly persons are not available.

The frequency of defecation in breast-fed infants during the first four months usually varies from two to four times daily; after this period the infant may be trained to defecate once daily. In a study of 527 males and 598 females ranging from 19 to 30 years of age, average 22, 96 per cent of the males and 92 per cent of the females defecated one or more times daily, the remainder from one to three times per week (192). According to Humphry's study (193), the bowels acted daily without assistance in 69 per cent of 824 persons between 80 and 100 years of age.

Constipation or colon stasis

It is impossible, for several reasons, to evaluate the extensive clinical literature on the subject of constipation, particularly in regard to its age incidence.

The term constipation has many connotations. It may be a real or an imaginary complaint of a patient; or it may be a symptom arising from a faulty diet, an atonic or hypomotile colon, nervous factors, a cathartic or enema habit, organic disease, etc. Further, many habitually and truly constipated patients give a history of the complaint as present since infancy or childhood. Also, by simply correcting the diet or by improving gastrointestinal hygiene, by removing cathartics and enemas, etc, frequently constipation, as a complaint, is relieved.

The only way that the true age incidence of that type of constipation which results from decreased motor activity of the colon might be determined would be to determine the gastrointestinal or colonic passage time after placing the subjects on an adequate diet associated with proper hygiene. Then, some such plan of investigation as outlined by Kegerreis (194) should be employed. The same plan would serve to determine the mean gastrointestinal-passage time of persons not complaining of constipation or gastrointestinal disturbances.

Constipation as a complaint

According to Grulee (195), constipation is one of the most common gastrointestinal disorders in infancy. It may be present in the youngest infant and exist throughout infancy and childhood. Griffith and Mitchell (196) state that age has little influence on the frequency of constipation in infancy and childhood. But data, worthy of consideration are not provided by the literature regarding the actual frequency of constipation as a complaint in infancy and childhood.

In a study of 1,082 persons, 582 females and 500 males, between the age of 19 and 30 years, average age 22, Walsh and his collaborators (192) found that 24.3 per cent of males and 38.1 per cent of females complained of constipation. The subjects surveyed were college and medical students and nurses; only about 2 per cent had consulted a physician directly be-

cause of the complaint, and none of the males and only 1 5 per cent of the females resorted to aperients oftener than once per week. Of course, all persons who complain of constipation do not show an "abnormal delay" or slow passage time (72 hours is considered a normal average) of barium through the alimentary tract; about one-fifth do not (184) On the other hand, Spriggs (197) found "abnormal delay" in the bowel in 1,000 patients out of 2,086 complaining of colonic disorders. Of the 1,000 only 764 complained of constipation. Of these 670 took aperients and 431 took them every day.

In 3,000 ambulatory adult patients living in New York and complaining of gastrointestinal symptoms, constipation was complained of in 46 5 per cent (184). More recently Kantor (198) has found that 54 2 per cent of 4,700 patients with dyspeptic symptoms complained of constipation of course, in some of these the dyspeptic symptoms were probably caused by a cathartic habit. Of those complaining of constipation, 93 5 per cent had had the complaint longer than one and one-half years Kantor has remarked, a remark that is not uncommonly made, that "in the majority of cases constipation is a life-long condition beginning during the youth or childhood of an individual". "Recent constipation" is at least five times as common in patients with alimentary tract cancers as in non-cancerous patients. However, the age incidence by decades of constipation as a complaint in Kantor's large series is not provided; in fact, the author has not been able to locate such data except that given above for the third decade. Humphry (193) states that very few (31 per cent) of the 824 persons above the age of 80 whose accounts he studied complained of constipation or took aperients. The foregoing reports vary somewhat from the report of Stroup (199) who found that 23 per cent of 134 men and 30 per cent of 96 women over the age of 60 suffered from constipation of more or less recent onset The average age of onset was 73 years in the males and 66 years in the females. Such variations in observations simply indicate that a careful study of many cases will be required before it can be concluded that ageing predisposes to the development of true constipation

It is believed that rectal constipation or impaction of feces in the rectum occurs not uncommonly in the aged (200). No data are available, however, to show that this condition is more frequent in the aged than in the mature adult. Miles (201) regards the development of the "pecten band" which limits the distention of the anal canal (202) to be a pathological accompaniment of advancing years.

Colonic malfunction

In the clinical literature dealing with the colon, the statement is rather frequently made that colonic malfunction (constipation, non-ulcerative

colitis, mucous colitis, or the so-called irritable or unstable colon) occurs most frequently from 20 to 50 years of age, generally in the fourth decade (203). The average age of Spriggs' (197) 242 cases of colonic malfunction was 44 for males and 42 for females. Eighty-three per cent of 200 cases of irritable colon observed by Jordan (204) occurred between the age of 20 and 60 years, and 68 per cent between the age of 20 and 50, the largest number occurring during the fourth decade. The fact that the old and young are so immune is attributed to the relatively tranquil conditions of living to which they are exposed. Ulcerative colitis has an age incidence not unlike that of functional disturbances of the colon. Brust and Bargen (205), who report on a study of 1,291 cases of ulcerative colitis, found that only 1.9 per cent of their patients were more than 60 years of age, and in these elderly patients the disease was relatively mild and limited to the distal colon.

Rectum

Hemorrhoids

Although hemorrhoids are associated with very definite local organic changes, some (206) believe that the frequent occurrence of the condition in man in contrast to lower animals is the result of the erect posture. In view of the general changes in the tissues associated with ageing, one might expect hemorrhoids to increase with age. Further, the opinion is widely held that hemorrhoids frequently result from constipation.

In regard to the general incidence of hemorrhoids, Kantor (184) made a study of 1,892 patients, the results of which give some indication of the occurrence of the condition as observed in a gastrointestinal medical practice, and not that of a proctologist. In this group 9 per cent manifested active hemorrhoids and an additional 17 per cent "healed hemorrhoids" on physical examination. His study showed further that hemorrhoids were as frequent in patients complaining of colitis (29 per cent), a condition associated with diarrhea, as of constipation (26 per cent), and that the condition was more frequent (38 per cent) in the presence of the cathartic habit than in any other group. Although with such evidence it is not possible to separate cause and effect, such evidence supports the opinion that the most important predisposing cause of hemorrhoids is the abuse of the rectum and anal canal with purgatives, or abnormal and frequent defecation, i.e., a functional disturbance.

Hemorrhoids are seldom seen in infants and children. The condition rarely occurs before the third year of age, and is usually associated with constipation in children (207). The condition was found to be present in 10.3 per cent of 283 males and 6.8 per cent of 305 females between the ages of 19 and 30. At the Mayo Clinic 3.4 per cent of all patients that enter

have hemorrhoids; whereas 48.8 per cent of those who present complaints referable to the bowel have hemorrhoids (208). In 23,443 patients with hemorrhoids the condition was found most frequently in the fifth decade Unfortunately, however, the true age distribution was not estimated (209)

It would appear that ageing may be a factor in increasing the incidence of hemorrhoids, but in view of the several other factors which predispose or contribute to their cause, it will be difficult to ascertain the truth regarding the effect of ageing per se on the condition.

Conclusion

On reviewing the evidence of ageing in the digestive system, one gains the impression that the organs of the system manifest physiological senescence. The evidence supporting such an impression is incomplete In most instances the evidence requisite for establishing the impression may be obtained readily by carefully planned, though time consuming studies

Death in the aged is apparently only rarely due to a wearing out of the organs of the digestive system. Most elderly persons die with a digestive system, which, when not directly affected by cancer, a toxic or an infectious process, is capable of functioning beyond the ordinary life span. Atrophic changes as a consequence of ageing or of injury by external agents may cause death or serve as a contributory cause. Whether these changes contribute to neoplastic growth, which is so common in the digestive system, is, of course, uncertain. Even though the consequences of ageing *per se* in the digestive system are not serious, it is striking that during life, symptoms referable to the gastrointestinal tract occur more frequently than those referable to any other system in the body. This is because the alimentary tract is so readily influenced reflexly by mental states and by disease elsewhere in the body, and because many of the symptoms of disturbance of the tract are functional in nature and tend to respond readily to diet and rest.

This is probably why Josh Billings wrote: "I have finally kum tu the konklusion that a good reliable sett of bowels is worth more tu a man than enny quantity of brains."

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21

LYMPHATIC TISSUE

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The lymphatic system is here considered as consisting of the sum total of lymphoid tissue in the body. Lymphoid tissue is found not only in clearly defined organs such as the lymph nodes, spleen, thymus and tonsils, but also as widely diffused masses of lymphocytes and lymph follicles in the walls of the digestive and respiratory tracts and less abundantly in many organs, including the liver, kidney and thyroid gland

The relationship of this tissue to other tissues in the different parts of the body varies greatly, the architecture of the various types of lymphoid organs is distinctive for each, and while some general functions almost undoubtedly are carried out by lymphoid tissue wherever found, the heterogeneity of structure suggests that the functions are various.

The problem of ageing in such a tissue are difficult both because of its manifold character and because of the rudimentary state of our knowledge of its various functions. That the ageing processes in lymphatic tissue do vary with the region and organ in which the tissue is found has been shown. Whether there is a fundamental similarity in manner of ageing, underlying the seeming differences, remains a subject for discussion.

The Cells of Lymphoid Tissue

The predominant cell of lymphoid tissue is the small lymphocyte. It is the typical lymphocyte of adult blood and lymph. This cell is characterized by a relatively small size (diameter 6 to 8 μ), by a scanty cytoplasm, occurring in fixed preparations as a narrow rim of basophilic substance about the nucleus, and by a spheroidal nucleus which is rich in chromatin and in which the nucleoli are inconspicuous. The basophilia of the cytoplasm is due to the relatively large amounts of ribonucleic acid (17) found

in the cytoplasm of all lymphocytic cells. The cytoplasmic basophilia of primitive or young bone-marrow cells is also due to the cytoplasmic ribonucleic acid (96).

The large lymphocytes, while they may occur anywhere in lymphoid tissue, are more common in the clear centers of the nodules. They may be as much as 15 to 20 μ in diameter and the cytoplasmic body is relatively large and appears as a much wider zone than in the small lymphocyte. The nucleus is more vesicular and one or more conspicuous nucleoli are seen. The large lymphocytes are strikingly similar morphologically to the hemocytoblasts nor is it possible to distinguish them by any differences in type of locomotion (24). According to the unitarian theory these types represent one and the same primitive cell form. According to this view, also, all lymphocytes retain the potency for forming blood cells.

The medium-sized lymphocytes generally are intermediate between the large and small lymphocytes in size, in relative amount of cytoplasm and in the qualitative characteristics of the nuclei and cytoplasm.

Other cells in lymphoid tissue include the fibroblasts which form and perhaps aid in maintaining the great network of reticular fibers among which the free cells occur; macrophages, either fixed, in which case they probably are simply fibroblasts with phagocytic ability, or free, in which case they represent large amoeboid cells; plasma cells, monocytes, and occasional myelocytes, granulocytes and mast cells.

Functions of Lymphatic Tissue and Lymphocytes

While certain concepts of the nature and function of lymphatic tissue and its cells have become widely accepted in pathology and clinical medicine, we find when we attempt to go more deeply into the subject and to establish a firm scientific basis for our conclusions that the problem presents exceptional difficulties. It has been suggested that the lymphocyte or lymphatic tissue is the source of the antibodies produced in immune reactions. This idea had been advanced by Loeb (61) and by Murphy (70) but experimental evidence was wanting. More recently such experimental evidence has been submitted by a number of authors. These include Ehrich and Harris (30, 31), Kass (51), Dougherty (28) and Dougherty and White (27). Most of this evidence is more pertinent as applying to "lymphatic tissue," which we have seen to be complex in its cellular composition, than to individual cell types.

Some of it, however, concerns the cells directly. Moor and Newport (69) found that mixing toxins from various bacteria with suspensions of lymphocytes led to a great reduction in the effectiveness of these toxins against animals. They believe that the lymphocytes play an important role in the immunity mechanism by affixing toxic products, particularly bacterial

toxins, and by producing antitoxic substances which may then be released either by a secretory process or by breakdown of the cells.

An hypothesis has been made that the cytoplasmic fragments which are shed from lymphocytes into the surrounding fluid may be the actual source of the antibodies. The fact that such a shedding occurs has been known for a long time, but Dougherty and White (27) have made the most important attempt to link this visible cellular phenomenon with the production of antibodies.

Any consideration of the role of lymphatic tissue in the economy of the body should take into account, it would seem, the large amount of this tissue normally present and the probability that its function is going on constantly. While a continuing effort at protection from foreign organisms and foreign substances is not improbable, in fact would seem to be almost a necessity, still the magnitude of such an effort and the mass of the tissue involved would seem to be surprisingly great if this is the major or only function of lymphatic tissue.

The lymphatic tissue appears to be very active in the *production of cells*, particularly of the small lymphocytes. They are poured into the lymphatic fluid, carried through the lymphatic channels primarily to the thoracic duct and emptied into the blood-stream in enormous numbers. Yoffey and Drinker (99) have shown that this is not a matter of lymphocytes migrating out from blood to connective tissue, then back to peripheral lymph, and so again to the blood. According to their studies on dogs and cats, only 1 out of every 30 lymphocytes entering the blood can be accounted for in this manner. The other 29 are newly-formed in the lymphatic tissue.

In all instances with which we are acquainted we find that when a tissue is producing new cells at a relatively rapid rate, as for instance in the epidermis, the new cells are being destroyed or consumed in some recognizable manner. In the case of the lymphocytes, however, there is no clearly recognizable destiny. It appears evident that they are formed in great quantities in lymphoid tissue and poured into the blood-stream. Yoffey *(100) says that enough thoracic duct lymphocytes alone enter the* blood stream to *replace those already there at least twice a day.* In regard to the fate of these blood lymphocytes three main possibilities may be presented: 1) they degenerate in the blood, 2) they differentiate into other cell types in the blood 3) they pass out into the tissues and there undergo a change, *either to exhaust their numbers as lymphocytes by degeneration,* migration to free surfaces or transformation into other cell types. There has been no convincing evidence of a degeneration within the blood nor of a transformation there into other cell types. There is abundant evidence that lymphocytes migrate into various tissues. This is particularly

well seen in the case of epithelial tissues since there is here no question of their having originated in such locations. Eberth (29), Von Arnstein (11), Paneth (73) and Beguin (14) were among the earlier authors who described lymphocytes in the intestinal epithelium. The question as to whether the lymphocytes actually pass through the epithelium and are cast out into the lumen has been answered differently by various authors. Guieysse-Pellissier (35) believed that they did not reach the lumen but that lymphocytes enter the epithelial cells and that a process of nuclear grafting occurs by which these wandering cells replace epithelial nuclei which dissolve into the cytoplasm. Bunting and Huston (23) stress the actual passage of lymphocytes into the intestinal lumen and their loss from the body in this manner.

Jassinowsky (48, 49), by the method of repeated irrigation with warm physiological salt solution and later counting of the elements from washes of the intestinal surface, found an extensive passage of lymphocytes into the lumen.

Hellman (41), on the other hand, believes that lymphocytes may remain in the epithelium for long periods to form a protective barrier.

Maximow and Bloom (64) say that many lymphocytes penetrate the epithelium and "occasionally even pass into the lumen" in the small intestine and that this phenomenon increases in intensity in the caudal direction, being greater in the large intestine.

Wolf-Heidegger (98) describes the lymphocytes as passing by amoeboid motion through the epithelial layer, making their way between the epithelial cells and into the lumen.

In a series of studies on this question (5, 9, 10) it has been shown that very large numbers of the lymphocytes which enter the epithelial layer by amoeboid motion become intracellular in position and that they degenerate within the epithelial cells or even undergo mitotic division there. Certainly large numbers of degenerate forms pass into the lumen but this seems to be a passive movement or an excretion by the epithelial cells. We have suggested (2) that some of the dividing lymphocytes may actually differentiate into epithelial nuclei and use host cytoplasm in the formation of new epithelial cells.

Hellman's view that lymphocytes remain for long periods in the epithelium seems to us to be a probable circumstance on the villi, although even here examination of a few oil immersion fields generally will show some passage of lymphocytes through to the lumen. In the crypts the whole process is a more conspicuous one, with large numbers of lymphocytes undergoing changes in the distal portions of the epithelial cells.

Lymphocyte penetration of epithelium is found in many organs including the oesophagus, tongue, trachea and bronchi, ducts of various glands,

female reproductive tract, epididymis, ureter and bladder, as well as in the intestine (83).

We have found also that lymphocytes occur constantly in the epidermis of the rat and of man and actually constitute 1 to 4 per cent of the cells of the stratum germinativum (7). Here they appear to undergo a transformation to clear cells and even on to epithelial cells.

We have stressed the matter of lymphocyte migration into epithelium since it offers one definite way in which we can "see" the lymphocytes being used up, either by degeneration or, in our opinion, also by differentiation into other cell types.

The multipotential characteristics of the lymphocytes, their ability to differentiate into other cell types, has been demonstrated beyond any reasonable doubt, at least for tissues other than epithelial. Observations made both by study of fixed sections and of tissue cultures have shown that the small lymphocytes may develop into macrophages (65, 77), fibroblasts (18) and polymorphonuclear granulocytes (19, 56, 94). If in addition they furnish new epithelial cells, they may be considered as of an almost totipotent nature, primitive replacement cells of inestimable usefulness to the organism.

These two great roles 1) of defense and 2) of differentiation to new cell types, represent the functions assigned to lymphatic tissue and lymphocytes by the majority of authors today. The evidence for each has been obtained by various workers and by various means. They do not seem to us to be in any way mutually exclusive conceptions but rather to fit rather well and logically into the pattern of the life of the organism.

Many other less inclusive roles have been assigned to the lymphocyte, some of which are related to the functions above mentioned. These include a lipolytic activity (15), resistance to cancer (70, 72), lysis of dead cells and synthesis of nuclein, stimulating mitosis (78) and carrying of hormones (20).

Simple Collections of Lymphoid Tissue

In many places in the body small collections of lymphocytes are found. These have been designated according to their location as peritoneal, pericardial, peribronchial, perivascular, subpleural, etc. While these in general are considered as somewhat transitory structures which may come and go during the life history, certain regions show them more conspicuously and more consistently in older individuals. This has been found to be true of the lymphoid accumulations about the hepatic trinity in the periportal canal of the liver (8) Wallbach (92) has investigated the etiology and development of such cell masses in the liver. According to him, they represent compensatory growths of splenic tissue brought about when such tissue

is needed in larger amounts. He believes them to be colonies arising from lymphocytes and reticular cells which have come to the liver through the portal circulation from the spleen. They can be produced experimentally by an increase in the amount of foreign albumen, by infections and by arsenic poisoning. The colonies grow in size both by the accumulation of new cells and by cell division. Their growth apparently leads to destruction of liver cells as the colonies replace portions of hepatic tissue.

In a study of the age changes in the parotid glands of the rat, accumulations of diffuse lymphoid tissue and occurrence even of small solid nodules amid the glandular tissue were seen as common occurrences in senile animals (3). Again, this seems to indicate probable colonization and local proliferation. The same phenomenon has been found recently both in parotid and submandibular glands in many older human subjects (4). Kingsbury (55) had pointed out the occurrence of lymphatic tissue and its association with degenerative processes in the small glands of the mouth, larynx and laryngopharynx in the cat. In his material, as in ours, such tissue usually was found in close relationship to the ducts and vessels in the connective tissue.

The other scattered accumulations of lymphoid tissue require further investigation before much can be said of their relationship to age.

Solitary and Aggregated Lymphatic Nodules

While the simple accumulations of lymphatic tissue which we have described above occasionally show nodular formation, they usually are not thus organized. In many parts of the body, however, particularly in relation to the mucosal surfaces of the gastro-intestinal and respiratory tracts, fully developed nodules are found in abundance, often showing a darker mass of small lymphocytes peripherally and a light center which has been called variously a germinal center or a reaction center.

Few data are available on age differences in these solitary nodules. In fact, it is not known whether they are in general constant elements or whether they may disappear and be replaced at intervals through life. As a statement concerning the alimentary tract in general we find that Ivy (47) says (referring to the appendix): "Its content of lymphoid tissue is said to diminish with age as is generally true of lymphoid tissue throughout the body and in *the alimentary tract*." (italics ours).

The same lack of knowledge is found in regard to the lymphoid tissue of the lower part of the respiratory tree. Macklin and Macklin (62) say, in regard to the lymphoid tissue in the tunica propria of the bronchi and bronchioles: "Doubtless senile atrophic changes involve this layer, along with the others." On the other hand, the evidence for the lung itself, as cited by these authors from Miller (67, 68) is that of a very substantial in-

crease in amount of lymphoid tissue in the peribronchial, perivascular, septal and subpleural locations. There even is evidence that new lymph nodes are organized from some of this lymphoid tissue, for such nodes occur farther down the bronchial tree as age advances.

Williams (97) has described solitary lymph nodules as of rather common occurrence in the bone marrow from various parts of the human skeleton, including the femur, humerus, ribs and vertebrae of different individuals. These follicles show no clear centers. They are formed more often in persons over 40 years of age. In 202 persons over 40 they were found in 32 per cent of the cases while in 28 persons under 40 they were found in 10 per cent (3 persons). Apparently, they have no pathological significance.

The next stage of organization of the lymphoid tissue appears to be as aggregations of the lymphoid nodules. These aggregations are seen as the Peyer's patches of the ileum and as the symmetrically arranged nodules of the vermiform appendix. Several studies on the lymphatic tissue of the appendix at different ages have been made. According to Bernardo-Comel (16), the maximum amount of lymphoid tissue in this organ is attained at the age of 13 to 17 years and maintained until the age of 20. With advancing age the amount diminishes, this process beginning at the tip and *progressing* toward the cecum. The clear center diminishes in size relatively more rapidly than the rest of the nodule. In the 60 to 70 year age group the lymphoid tissue was found in greatly reduced quantity and consisted of isolated elements near the proximal end, seldom showing clear centers.

Stefanelli (88) found that as a rule there are no follicles present after the age of 75 years although in certain cases the appendix is still rich in lymphatic tissue.

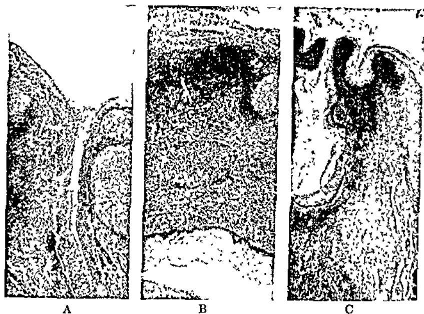
Hwang and Krumbhaar (44) found the weight of the lymphatic tissue highest in the first decade, decreasing to a minimum in the seventh decade but then seeming to continue at the same low level in still older persons.

We believe that in considering age changes in the lymphatic tissue in [illegible] very [illegible] age [illegible] nges in the lymphoid tissue in the wall of the appendix need not, then, be entirely representative of a general trend in the walls of the various other portions of the alimentary tract.

The Tonsils

A stage beyond the aggregates of lymphatic nodules are the organs known as tonsils. They consist of aggregations of such nodules but they show a higher degree of organization and bear also a more definite relationship to surrounding structures, both through the possession of a frequently well

developed connective tissue capsule on the deep aspect and through a *peculiar relationship to the overlying epithelium on the superficial aspect.* Waldeyer's ring of lymphatic tissue about the pharynx includes the three types of tonsils, the palatine tonsils, the pharyngeal tonsil or adenoids,



eliminate
is disease

and the lingual tonsils, as well as continuous masses of diffuse lymphatic *tissue between them.*

All of the tonsils present deep crypts of the epithelial covering with stratified squamous epithelium lining those of the palatine and lingual tonsils, and pseudostratified ciliated columnar epithelium lining those of the pharyngeal tonsils. The epithelium is distinguished by a migration of enormous numbers of wandering cells, lymphocytes and polymorphonuclear leucocytes, into and through it. Frequently this process is so intense that the epithelium takes on a vacuolated reticular appearance and

it becomes difficult to distinguish the boundary line between it and the underlying tissue.

While it is customary to speak of the *migration through the epithelium* as though it were an *activity of the leukocytes*, Kelemen (54) offers evi- [illegible] transfer is *primarily* a passive one, that fibrillar cages con- [illegible] into the *epithelium enclosing* [illegible] ections

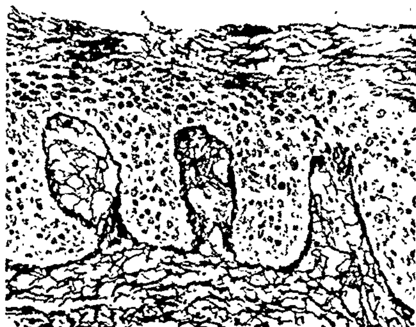


FIG. 2 Epithelium of palatine tonsil, showing projection upwards of reticular meshworks. These seem to carry lymphocytes into the epithelium, then liberate them. Gomori impregnation (Kelemen (54)).

often touch even the most *superficial* layers of the epithelium. *In the deeper* parts of the epithelium *these* structures are slender *and* tube-like but they expand to cyst-like *formations* as they proceed *upward*. Finally they reach the *lumen* and the leukocytes are discharged *to* pass along threads of fibrin to the mouth of the crypt.

A number *of studies* have been made on age *changes* in the tonsils. Hieronymus (43) studied the palatine tonsils from 100 human autopsy subjects. He found a rapid rise *to* a *maximum* size at about *the* twelfth year, a maintenance of a *fairly* constant size until *35 to 40 years* of age, then another levelling off *until* about *70* years, *when a second* decline sets in. *The* clear centers *of the nodules do not appear until a few months*

after birth, according to Pol, (76) third to twelfth month; Barnes (13) "by the sixth month," and Kniachetsky (57) sixth month. They are at their maximum development about the time of puberty.

In regard to the histological and cytological details of ageing of the tonsils, several workers have made contributions. Wessel (95) found a great decrease in the numbers of lymphocytes migrating through the epithelium in later life.

Kelemen (53) has described the palatine tonsil in the sixth decade of life.



FIG. 3. Palatine tonsil of a senile subject. The organ is reduced to a single open crypt and adjacent structures (Kelemen (53)).

Involution in these organs is, he says, an atrophic process. There is no sign of a change of their cells or tissues to a functionally less active form but only a decrease in number of the elements. The capsule remains well defined behind even the last remnant of the organ. No senile fibrosis occurs within the tonsil, nor are formations of bone, cartilage or cysts any more common in older adults than in younger ones. However, he does describe the last stages as showing only scattered accumulations of lymphocytes in a scar-like tissue. The crypts tend to be erased by either one of two methods. In the first, they seem to become narrower and finally to "melt into" the surrounding lymphoid and connective tissue. In the second, an eversion of the crypt occurs so that the formerly cryptal epithelium becomes surface epithelium. It still retains its highly reticulated appearance, how-

ever. The lymphatic parenchyma continues to send leukocytes through the epithelium.

In a further study Kelemen (52) made clinical examinations of the tonsils of 309 older patients, including 50 men and 50 women in each of the seventh, eighth and ninth decades of life and an additional 9 patients from 90 to 103 years of age.

While a steady decline in size of the tonsils in old age was noted, com-

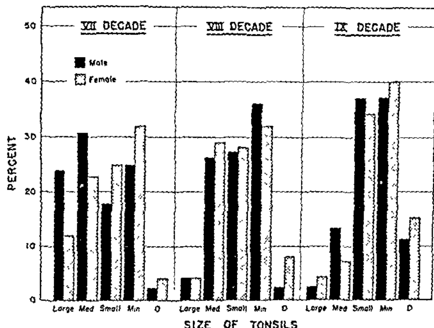


FIG. 4 Stereogram to show relative numbers of palatine tonsils of different sizes in the 7th, 8th and 9th decades and their division according to sex (Kelemen (52)).

plete absence was rare. The fossa always remained as a more or less spacious niche. Characteristic involutionary forms include 1) the narrow vertical ridge of tonsillar tissue, 2) the large drop-like remnant in the lower part of the niche and suspended by a pedicle-like structure and 3) the small crater surrounding a last-remaining cryptal opening. Local inflammations, tonsillar and peritonsillar, are infrequent but when they occur they take the same course as in other age groups.

Kelemen believes that there is a period of high tonsillar activity with *even a "slight possible temporary enlargement"* around the sixth decade, corresponding to the similar period before puberty. He concludes that the tonsils frequently are of clinical importance in older persons.

In regard to the pharyngeal tonsils, our data are more scanty. It has been generally accepted that they are largest in children. Earlier authors give the specific age of highest development variously. Todd (91) has studied them by use of *the standard roentgenogram. He finds them developing* at about 12 months, increasing in size until 3 years, usually remaining stationary until adolescence and then undergoing a gradual regression. In old age the region may show sparse aggregations of lymphoid tissue scattered over the mucous membrane (66).

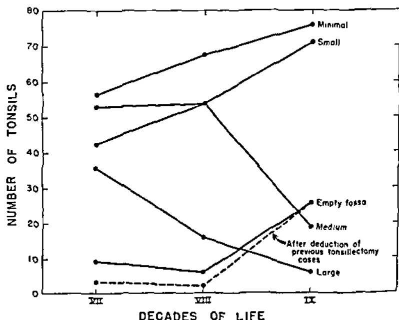


FIG 5. Graphic presentation of size of palatine tonsils in 7th, 8th and 9th decades of life (Kelemen (52))

The lingual tonsils, according to Rossing (81) are both the last to develop and the last to undergo regression. The pharyngeal tonsils are first and the palatine tonsils intermediate in these respects, so that Rossing believes that he has demonstrated a cranio-craudad progression in development and regression of the elements of Waldeyer's ring.

THE THYMUS

We place the thymus next in our consideration of the lymphoid structures as it is an organ in which the two major elements are still the epithelium and the lymphocytes (38). Gregoire (33) has shown how in grafts of thymic tissue the epithelial portion becomes compact, *then is invaded* and reticularized by lymphocytes of the host. By irradiating the *thymus*

before transplanting he was able to destroy the autochthonous thymocytes or lymphocytes. He does not believe that the thymocytes of the normal

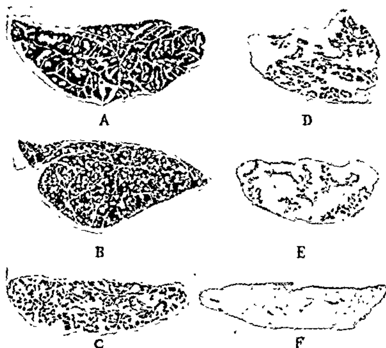


FIG 6. Histology of thymuses at various ages showing age involution (Hammar, (38).

A Male infant, died during delivery. Thymus weighed 15 64 g. The darker portion is parenchyma (82 per cent), the lighter portion is connective tissue.

B A healthy boy of 6 years, drowned Thymus weighed 23.0 g.; parenchyma, 71 per cent.

per cent.

E. A man of 48, died from carbon monoxide poisoning. Thymus weighed 15 g, parenchyma, 12 4 per cent

younger one.

thymus, then, are derived from the epithelial elements, but he apparently has proved their character of true lymphocytes. On the other hand, Bailiff (12) says that in regeneration of the thymus the early reconstruction of the thymocytic portion is carried out almost exclusively by a process of epithelial cell transformation. Murray (71) believes that he has seen

and recorded in pure culture of rabbit thymus epithelium a differentiating mitosis in which the two daughter cells from an epithelial cell were, respectively, another epithelial cell and a lymphocyte.

The thymus is, therefore, not only an organ which has been very puzzling in regard to its physiological function but which offers a field for investigation of some fundamental problems in the relationship of cell types, particularly of the lymphocyte to the epithelial cell.

Hammar (37, 38) has carried out the most intensive investigation of age changes in the thymus. In a study of the thymus glands from 345 human autopsy cases (38) he shows that the human thymus grows rapidly through fetal life, continues to increase in absolute weight up to a maximum at the

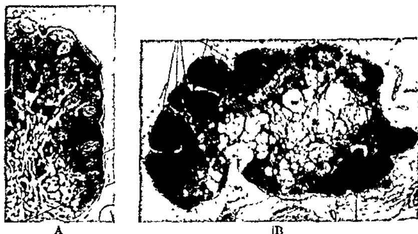


Fig. 7. A. Part of cross section of a fully developed human lymph node (Hellman)
B. Senile human lymph node showing fatty infiltration (Hellman)

sixth to tenth year, with a slow decline after the 16 to 20 year age group has been passed.

While there has been a somewhat general impression that the thymus undergoes complete or almost complete degeneration, this does not seem to be the case. Bremer (22) states that while the thymus begins an involution about the time of puberty it does persist through life. Boyd (21) says that after 11 years of age the weight of the thymus decreases slowly to about the same weight which it had at birth (15 g.). Boyd collected 207 cases of death from accidental causes within twenty-four hours of injury. The cortex began involution at 4 years in her group, while the medulla, with the Hassall's corpuscles, began involution at puberty and the replacement of thymic tissue by connective tissue and adipose tissue continued into old age.

The cortex in early life contains many closely packed lymphocytes. As

age advances and the cortex atrophies, the distinction between it and the medulla becomes less marked and finally cortical tissue often appears only as darker areas in the narrowed medullary strands. The great degree of variation in the histological picture and in the degree of involution at different ages must, however, be stressed.

The peculiar bodies which have been designated as Hassall's corpuscles are seen first in the fetus as a few small rounded bodies of 12 to 20 μ in diameter. They increase rapidly both in number and in size. By the end of puberty some reach a diameter of 800 μ. They seem to decrease gradually in size, so that from the seventh decade none surpasses 300 μ in diameter. They decrease also in number as the destruction of both cortical and medullary parenchyma proceeds.

The value of the weight of the thymus as given in deaths due to various diseases probably is low as compared to the normal figure for the given age, since lymphatic tissue tends to be reduced rather rapidly in manition. In fact it has been said that the large thymus of status thymo-lymphaticus may be simply a normal thymus which, due to the sudden death, has not had an opportunity to decrease in size.

Studies of age changes in the thymus have been made on several of the lower animals. Soderlund and Backman (87) studied 80 rabbits of known age and found that, as in man, the thymus lost weight with age in spite of infiltration by adipose tissue. Great individual variation was present. After the age of 2 years the cortex was practically indistinguishable from the medulla.

Syk (90) found that Hassall's corpuscles in the rabbit increase in size and number up until puberty, then decrease but at the age of 2 years are still large and numerous. Lindberg (60) found that the first appearance of spermatozoa in the male rabbit and of fertility in the female rabbit coincided with the beginning of involution of the thymus gland and with the time of maximum number of lymphocytes in the blood.

In the rat also the thymus appears to reach its maximum weight at the time of rapid increase in the size and development of the gonads. According to Donaldson (26) the maximum is at 82 days, while at 400 days the thymus weighs only 14 per cent of this maximum. As in man, the thymus seems to persist through life, undergoing a slow atrophic change. Here too the atrophy involves chiefly the cortex, the lymphocytes being replaced by fat and connective tissue.

In the guinea pig the thymus reaches its maximum size when the animal weighs 200 to 300 g. (74). Involution begins at the time of beginning of sexual maturity (50). In the horse Shimpei (86) found that involution begins in the cortex with atrophy of the lymphoid tissue and replacement by connective tissue. The medulla shows the beginning of involution by

an increase in size and number of Hassall's corpuscles and by fatty infiltration. Eosinophils, originally only in the medulla, are later found in the cortex as well and frequently in a degenerate condition.

It is of some interest to note that a sex difference in the thymus of the mouse has been described by Masui and Tamura (63), the gland of the non-pregnant female averaging 0.038 g. as against 0.021 for the male. Schirber (84) found a heavier thymus in the female than in the male goat. In the 462 goats which he studied the thymus in females weighed 30.5 g. at birth, 35.5 g. at 3 years, and fell to an average of 5.4 g. at 5 to 11 years. The thymus in males weighed 23.4 g. at birth, 23.0 g. at 3 years and 11.9 g. at 5 years.

Waschinsky (93) found, however, a greater weight for the thymus in male than in female pigs. He studied glands of 110 pigs. Here again maximum weight occurs at the age of beginning sexual maturity—6 months. Krupski (59) found that in cattle the weight of the thymus increases for 7 to 8 weeks after birth and is in full regression by 8 to 12 months. In dogs atrophy begins at 2 to 3 months, according to Hammar (38).

The thymus is one of the few organs in which some study of age changes has been made in classes of vertebrates other than the mammals.

Hammar (38) states that in fishes the involution of the thymus begins coincidentally with the arrival of sexual maturity. Glandular and mucoid masses appear and the perivascular connective tissue is thickened and may become hyaline. Lymphocytes decrease in number, particularly in the cortex. Picchio (75) found an appearance of cavities of large size in the thymus of Lophius budagassa and a loss of distinction of cortex and medulla with advancing age.

In frogs of 50 g. and more Hammar (38) found also mucoid areas in the thymus. The cortex was thinned in older (heavier) frogs and the pigment and perivascular connective tissue increased in amount. Cysts were seen but they occurred also far down in the weight scale.

In the birds involution of the thymus seems to begin relatively late. Hammar (ibid.) found the organ to be of about the same size in all of the hens studied, although in older birds the cortex did become thinner and developed epithelium-lined lumina. Even at 7 to 12 years, however, the medulla remained well developed, although the cortex was much reduced. Riddle and Frey (80) found regression in the thymus of the dove beginning at 3 months.

The Lymph Nodes

The number of lymph nodes in the adult human body probably amounts to several thousand. Hellman (40) was able to demonstrate 200 to 500 nodes in the mesentery alone. Lymph nodes appear in the fetus first as

primary groups of axillary, inguinal, cervical and retroperitoneal chains. Later, secondary groups including the epitrochlear, popliteal, intra-mesenteric and para-aortic make their appearance.

There is considerable variation of opinion among earlier authors as to when the lymph nodes attain their maximum size. While many have stated that they attain maximum size in childhood, others (89) specify this as maximum *relative* size referred to body size. Grossman (34) said that the growth and involution of lymph nodes parallel those of the body as a whole. Gundobin (36) stated that maximum size is attained during infancy. It has been generally agreed that the nodes at all ages retain their ability to respond to infection by proliferation of both reticuloendothelial cells and lymphocytes.

It would seem that a study of age changes in lymph nodes of laboratory animals would avoid some of the complications necessarily involved in the study of human autopsy material. Hellman (42) made a very thorough study of the nodes from various regions of the body from 100 rabbits, divided into 12 age groups. The study is, however, primarily quantitative, and histological and cytological features are not described to any great extent. Hellman found an increase in the mass of the nodes up to 5 months of age, then a decrease. Peculiarly, however, a second growth period occurred for the cervical and popliteal nodes, with a final decline beginning after one year The nodes of the oldest rabbits ($3\frac{1}{2}$ years) weighed only about half that found in the stage of their maximum development.

The view that lymph nodes in young animals are larger than those in old is accepted by Ellenberger and Baum (32), who dealt with domestic animals in general

Concerning reports on age changes in the lymph nodes, Denz (25) states that they are "fragmentary, ill-co-ordinated and often contradictory". Denz studied over 300 human lymph nodes collected from 150 autopsies, and in addition a small number of normal glands obtained by biopsy. About a third of the glands were from accident cases, another third from acute medical and surgical cases, and another third from cases of chronic disease. Over 200 of them were from the deep cervical and axillary groups. The rest were mesenteric, axillary or bronchial. Several fixing and staining methods were used and over 50 of the nodes were studied in serial sections, models being constructed in some cases

Denz devotes a good deal of his discussion to a consideration of the normal structure of lymph nodes in general. In superficial nodes, such as the inguinal, according to him, the lymphoid tissue consists of a thin layer covering a large fibrous hilum. In deep nodes, such as the deep cervical, there is a greater mass of lymphoid tissue and only trabeculae from the relatively small hilum penetrate into it, carrying the blood vessels.

He finds germinal centers appearing during the first years of life and beginning to retrogress at puberty. He believes that if cyclic changes occur in such centers in the absence of inflammation, such changes must be slow and unimportant.

The lymph nodes show differences in age dependent upon their anatomical position and function, although both superficial and deep nodes reach a maximum development during childhood and decrease in size after puberty. In the inguinal nodes the germinal centers and the trabeculae seem to be poorly developed at all ages. After puberty, the cortical tissue decreases in amount. In senility the cortical tissue consists of islands *surrounded by medullary tissue. Although there is a shrinking of lymphoid* tissue, the size of the node does not change greatly as the hilar connective tissue growth generally compensates for the change in the lymphoid tissue.

The nature of the hilar tissue appears to depend on what is available as replacing tissue in the individual. In cases of adiposity, for instance, adipose tissue replaces the lymphoid tissue. In the spare individual fibrous tissue is more common. In starvation or wasting diseases the hilum becomes cystic. Denz says (p. 585), "The connective tissue is greatly reduced and in its place great lymph-containing spaces are found, but the lymphoid tissue is still peripheral in arrangement."

The deep cervical nodes during childhood show well-developed germinal centers and trabeculae. While there is some decrease in size after puberty due to retrogressive changes in the germinal centers, the late changes are less marked than in the inguinal node. In extreme old age the deep cervical node may resemble that of the fetus in its simplicity of structure, for the cortex and medulla may again appear as continuous units, without nodules, and trabeculae are almost lacking. The medullary reticulum may show some fibrous change but that of the cortex is, he says, "without collagenous taint".

At any period of life a local inflammatory stimulus may cause the node to take on again the characteristics seen in childhood.

Andrew and Andrew (6) studied the deep cervical nodes from a series of 100 Wistar Institute rats. They find that the age differences in the nodes are great enough that one can identify with considerable accuracy, by histological study, nodes from young, middle-aged, and senile rats. In the 21 day animals the nodes show a great preponderance of cortex over medulla. The clear centers of the nodules are only beginning to develop at this age. The young mature and middle-aged rats show a gradually increasing size of the medulla with a concomitant decrease in width of the cortex. In the senile animals the medullary sinuses frequently extend almost to the capsule.

A conspicuous feature of many of the nodes in senile animals (about 37 per cent) is the presence of large fluid-filled cavities, evidently arising due to atrophy of the lympho-reticular tissue (fig. 8B). However, in spite



FIG. 8A. Lymph node of a middle-aged rat (302 days) Distinction between cortex and medulla is sharp Reaction (germinal) centers are present. (Andrew and Andrew (6))



FIG. 8B. Lymph node of a senile rat (1,000 days) Distinction between cortex and medulla is vague. A large cavity is present on the left-hand side. The sinusoids are wide and there are no reaction (germinal) centers (Andrew and Andrew (6)).

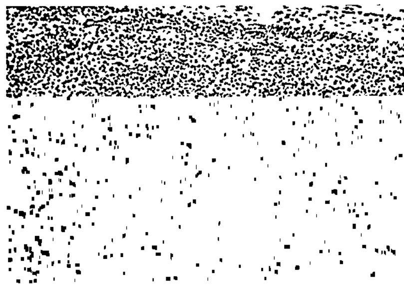
of such atrophy, the mean weight of the nodes in the group of oldest specimens is significantly higher than that in the younger adult rats. This seems *to be due to a hypertrophic change in these organs occurring along with* the alterations which, by themselves, would lead to atrophy.

The more minute or cellular details of the nodes of senile rats differ from those of younger animals both in the cortex and in the medulla. While in the cortex of the younger rats the closely packed cells are definitely

small lymphocytes, in that of senile animals the majority of them frequently are more properly designated as plasma cells, at least in regard to the greater abundance of the cytoplasm and the eccentricity of the nuclei.



FIG. 9A. Cortex of a lymph node of a 300 day old rat. The generally compact appearance is seen. A large reaction center is present in the field (Andrew and Andrew (6)).



many
mble

In the medulla in younger rats there are relatively few free macrophages, most of the cells being stellate in form and connected to the reticular framework by their extended processes The sinuses generally are well bridged by reticulum. In the senile rats the sinuses are much less frequently

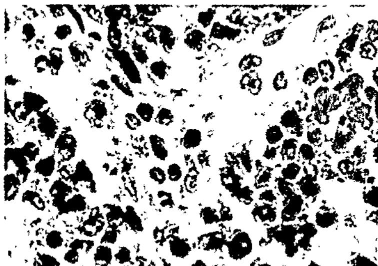


FIG. 10A Medulla of a lymph node of a 300 day old rat Sinusoids are narrow and there are few macrophages (Andrew and Andrew (6))

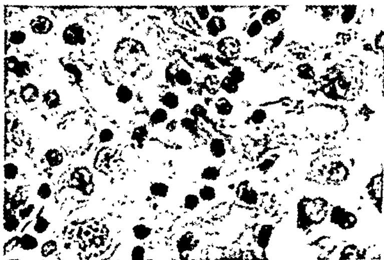
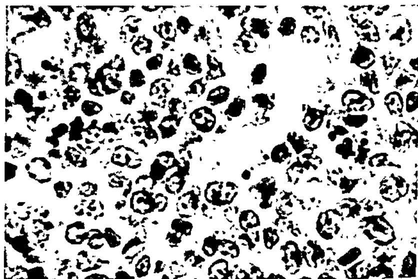


FIG 10B Medulla of a lymph node of a 900 day old rat The wide sinusoids contain many large macrophages which show in their cytoplasm pigment, nuclear debris and vacuoles (Andrew and Andrew (6)).

bridged by reticular cells and fibers. The number of free macrophages is much increased. The cells are large, rounded, and show many indications of functional activity (fig. 10B). Frequently most of the cell-body is filled by large globular masses of deep-brown pigment. In many cells large clear vacuoles occur. In others the bodies of whole lymphocytes or neutrophils or masses of nuclear debris are seen. The numbers, size and appearance of functional activity of these cells in senile animals are so distinctive as to enable one to identify a node as from a senile animal by examination of a single high-power field.



Fibrosis is never of great extent in the nodes In a number of the senile nodes, however, some fibrotic change is seen, particularly near to the hilum where masses of plasma cells seem actually to coalesce, fibroblasts then appearing in these masses and fibers being laid down. Neither fibrosis nor adipose tissue invasion appears to play any important role in the filling in of spaces left by atrophy of the lymphoid tissue itself in the rat.

The findings of Denz for the human nodes agree well in many respects with those of Andrew and Andrew for the rat nodes. In both cases a decrease particularly of the cortical tissue is noted with advancing age. This decrease is recognized on a histological basis but in the human nodes we do not have weights which might tell us whether a compensatory hypertrophy is occurring, as seems to be true in the rat.

In the human nodes, according to Denz, the type of tissue which replaces lymphoid tissue seems to vary in accordance with what is available. Thus, in obese individuals it is adipose tissue; in spare individuals it is fibrous tissue; while in inanition there is no replacing tissue and parts of the lymph node show large lymph-containing spaces. The last-named condition is characteristic of the senile rats in the series of Andrew and Andrew. Yet in these animals adipose tissue was abundant in others of the organs studied, as in the parotid glands (3).

The cellular changes both in cortex and medulla are conspicuous in the rat. In man not much attention seems to have been paid to these details, and the problem would be somewhat more complicated in autopsy material than in the laboratory animal.

The Spleen

The spleen may be considered as the largest lymphatic organ of the body and the malpighian bodies are generally well-defined nodules of lymphoid tissue. Nevertheless, the peculiar arrangement of much of the lymphoid tissue in the spleen, scattered diffusely as a component of the red pulp and existing as adventitial sheaths for the extratrabecular arteries, makes a quantitative study of this tissue at different ages a difficult matter.

Hellman (39) carried out a quantitative study on the spleens of 100 human subjects, ranging from newborn to 84 years of age. He used excellent material, all of the cases representing accidental sudden death, suicide, or murder, and it is of interest to note that it required almost twenty years for him to collect all of the specimens. All of the subjects died within twelve hours of the injury, most of them instantaneously.

Hellman was interested primarily in the weight relationships of the red and white pulp, the secondary nodules, capsule, trabeculae and blood vessels. He found the average weight of the spleen increasing up to an age between 20 and 30 years and showing a definite decrease only after 50 years of age. The lymphoid tissue (follicular pulp being meant in this instance) increased until directly after puberty (16 to 20 years) at which time the age involution begins. The decrease seemed to continue until the most advanced age. At the age of 5 years the lymphoid tissue amounts to 22 per cent of the weight of the spleen, at 10 years to 17 per cent, at 20 years to 12 per cent, at 60 years to 7 per cent and at 84 years to only 5 per cent. It must be noted however, that there were in Hellman's series only 5 cases over 50 years of age. It should be noted also that the figures given represent percentages only and must be taken in connection with the total spleen weights in order to arrive at the true amount of follicular lymphatic tissue in the spleen at any given age.

Hellman found the secondary nodules best developed at 1 to 10 years

and their average number highest at this time. By the age of 20 years they are already much less conspicuous. Their fullest development, therefore, is somewhat in advance of the fullest development of the lymphoid tissue of the follicles.

The connective tissue (in this instance including the capsule, trabeculae and blood-vessels) shows some increase in percentage weight with age. In the 21 to 30 year group it constitutes 6.91 per cent of the total weight, while in the group over 50 years old, it is 11.07 per cent of the total weight.

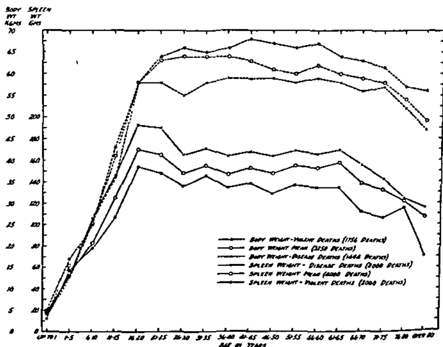


FIG. 12. Means of spleen weights and body weights in 2000 disease and 2000 violent deaths and combined (Krumbhaar).

Hwang, Lippincott and Krumbhaar (45) made a similar study, using spleens from a larger number of persons but again only from persons dying *violent deaths shortly after the violence occurred and excluding* all spleens showing any signs of disease. Microscopic fields of the organ were projected and the outlines of the malpighian follicles and of the intervening tissue were drawn on paper, the areas then being measured with a planimeter. Knowing the spleen and body-weights it was then possible to get an approximate weight for the follicular lymphatic tissue in the spleen and also its ratio to the body weight at the different ages. In this way 300 cases of violent death distributed in 9 age groups from birth to 70 years and over were analyzed. As in Hellman's work, the percentage of lymphatic tissue

was found to be low in the first year (4.5) although the relative number of follicles was then at a maximum. The maximum percentage of lymphatic tissue is reached in the first decade (10.8 per cent), again agreeing with Hellman. However, whereas in Hellman's study the percentage then fell steadily throughout life, their curve dropped sharply to 7.7 per cent in the 11 to 30 age groups, then fell more gradually in the next two age groups. In the 50 to 70 year group a slight rise occurred, while in the oldest group (all cases over 70) the figure fell to 5.8 per cent. These authors believe that a possible increase of lymphatic tissue in late middle age, associated perhaps with increased resistance to various infections, is indicated by their figures.

Krumbhaar and Lippincott (58) have made a study also of the total weight of the human spleen at different ages. They point out the great variation in figures found by earlier authors. Schridde (85), for example, gave as the normal weight of the spleen 115 g while Hyrtl (46) had set it at 250 to 300 g. Rossle and Roulet (82) studied spleen weights in 802 subjects, 569 males and 233 females. They found a maximum weight of 169.1 g. for males in the third decade and of 153.7 g. for females in the fourth decade. In the seventh decade average weight of the spleen was about 112 g. and for all persons over 70 years of age about 103 g. Spleens from 2 persons over 90 years of age averaged only 65 g.

Krumbhaar and Lippincott (58) analyzed 2,000 routine autopsy cases, omitting those which at autopsy or during histological examination showed any considerable splenic changes, particularly such as might lead to splenomegaly. The subjects were divided into 18 semi-decades, ranging from birth to 95 years.

The 16 to 20 and 21 to 25 age groups had significantly heavier spleens than those in any other groups. However, the lower weight level of the 26 to 30 year age group was maintained with little change up to the sixty-fifth year, after which a sharp loss occurred. The authors say that while body weight seems to have nothing to do with the peak weight from 16 to 25, it is "presumably a factor" in the final decline.

These authors assembled data also on spleen weights of 2,000 persons dying violent deaths. They state that they realize that even in such cases there are many unknown factors and that even when full allowance is made for the possible inclusion of undetected abnormalities, the normal spleen must be recognized as one of the organs most variable in size and weight. The graphs of the mean spleen weights of the 2,000 disease deaths and of the 2,000 violent deaths show a very considerable degree of parallelism. The former probably average too high, they say, and the latter too low, so that the middle curves in the graph, representing the data for all 4,000 cases, probably come nearer to giving the true picture.

Study of the ratio of the spleen weight to the body weight in all 4,000

cases shows it to be highest in the earliest age group. From there on the slope of the ratio is slightly but "not significantly" down, except for a plateau in the groups between 51 and 65 years where the ratio is significantly higher than those of the age groups on either side. This again would seem to be an indication of a probable increase in lymphatic tissue at this period of life. The very oldest spleens were light in weight, but while fibrosis, arteriosclerosis and atrophy (low weight) are the rule in the spleen of the aged, the lymphatic tissue may persist in considerable amounts even in extreme old age.



FIG. 13 Two large macrophages from a reaction center in the spleen of a 150 day old rat Such cells have many fragments of lymphocytes and even whole lymphocytes *in their cytoplasm (Andrew (1)).*

They sum up the results of their studies on the weight of the human spleen and on the percentage of lymphatic tissue in it at various ages as follows: *"the spleen appears to grow parallel with the growth of the body during childhood, but reaches its maximum weight (170 grams) earlier (i.e., in the 16 to 20 age group as opposed to 26 to 40 years for the body weight). From the ages of 26 to 65, its absolute weight remains approximately unchanged, though, compared with the average body weight, the spleen weight falls slightly, except for the 51 to 65 age group where it rises significantly. After 65, both spleen and body weight fall steadily, the spleen weight more than the body weight, so that in the very old weights less than 100 grams are frequent.*

The lymphatic tissue in the Malpighian follicles, low at birth, quickly rises to a maximum percentage early in the first decade. It then drops, most sharply in the second decade, till the age of 50, when there is a distinct increase

lasting till about 65. Thereafter, it falls again eventually to reach a percentage similar to that of early infancy."

Both the spleen weight and the lymphatic tissue percentages show a marked individual scatter.

Little attention has been paid to the question of age changes in the spleen in laboratory animals. Andrew (1) studied the spleens of 100 Wistar Institute rats. These ranged in age from 21 days up to 1170 days. In the senile group (animals 800 to 1170 days in this study) there were 35 animals.

Qualitative as well as quantitative differences in the spleens from rats

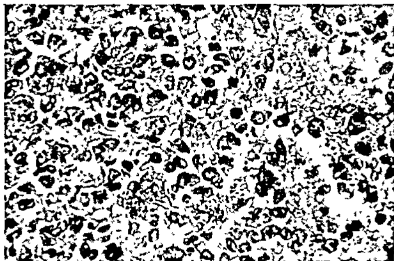


FIG. 14. Red pulp of the spleen of a 600 day old rat. The appearance is compact, with the sinusoids inconspicuous The macrophages, of which about two dozen are seen in the field, contain a golden-yellow pigment (Andrew (1)).

of different ages were found. In the immature rats (21 days) malpighian follicles are in process of formation and no reaction centers are seen. In young rats (50 to 200 days) reaction centers are numerous and well-marked. They persist in the rats of middle age (300 to 726 days). In senile animals reaction centers are lacking in almost all cases (32 out of 35 animals for the several large sections studied).

There is a decrease in amount of follicular tissue in old rats and a loss of distinctness in the separation of the two zones of the follicle as well as of the demarcation between red and white pulp. The follicles of senile animals often show several sections of thick-walled artery rather than the single section.

The red pulp of senile rats presents a conspicuous change consisting in a transformation from a predominantly compact, reticular type of

tissue to a predominantly sinusoidal type (figs. 14 and 15). This change would seem to be brought about by an actual metaplasia of reticular cells to endothelial cells with formation of new sinusoidal spaces from the open ends of the old ones.

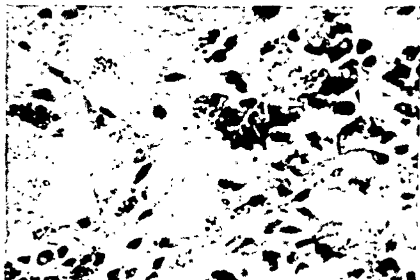


Fig. 15. Red pulp of the spleen of a 1,060 day old rat. The very loose appearance of the tissue is evident The macrophages contain a deep brown pigment, much darker than in young and middle-aged animals (Andrew (1)).



Fig. 16. A pigment-containing macrophage in the red pulp of a 150 day old rat. In young animals the stellate form of such cells is common (Andrew (1)).

In 21 day rats there are no pigment-containing macrophages. They make their appearance first in 50 day rats and increase in numbers per volume of spleen up into middle age. The variation in number in senile spleens, however, is very great. In spleens in which the architecture of the white pulp is largely destroyed they are scarce.

The red pulp in senile animals shows more degenerating pycnotic and fragmenting lymphocytes than are seen in young animals. These often are being phagocytized by macrophages. Plasma cells are more abundant in old rats.

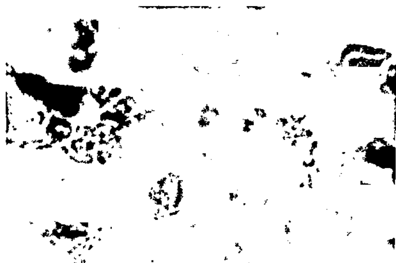


Fig. 17. A pigment-containing macrophage in the red pulp of a 1,000 day old rat. In senile animals such cells are more often without processes and with deeply-staining nuclei (Andrew (1)).

Megakaryocytes are plentiful in the spleens of young rats, undergo a sharp decrease in number at an early age but persist in fair numbers in senility. A megakaryocytic splenomegaly is seen in a number of old rats (16 per cent in this material).

The range in weight of the spleen in old rats is greater than in any of the younger groups and while a number of the senile spleens seem to be atrophic the average weight actually is greater than that for the young and middle-aged animals.

Summary

The lymphatic tissue, from its considerable abundance and widespread distribution in the body, as well as from its ready response to changes in the organism, would seem to be of very great importance. Two major

functions can be assigned to it: 1) defense against invading organisms and noxious substances and 2) the formation of cells with multipotent characteristics which by their differentiation give rise to macrophages, fibroblasts and other cell types.

Our survey of the present state of knowledge of age changes in lymphatic tissue has shown us that a large number of facts have been acquired concerning these changes. The picture, however, seems to be a complicated one and generalizations are not easily made.

While some authors believe that the diffuse lymphatic tissue in the tunica propria of various organs undergoes atrophic change in old age, there is good evidence that accumulations of lymphatic tissue make an appearance and increase in size in older individuals in the interlobular connective tissue of the liver, salivary glands and lungs. Lymphoid nodules are more common in the bone-marrow of old than of young persons. In some organs, such as the appendix, the nodules decrease in size and number in old age.

A definite involution in later life is seen in all three types of tonsils and consists in a simple atrophic process. Complete absence of the palatine tonsils in old people, however, is rare. There is evidence even of a slight temporary enlargement of the palatine tonsils around the sixth decade, corresponding to the similar period before puberty.

Present data on the thymus tend to show that it seldom undergoes a complete involution, that some thymic tissue persists even into old age. It is, however, the earliest of all of the lymphoid organs to show marked regressive changes and the greater part of its parenchyma becomes replaced by fat and connective tissue. Its history appears to be tied up with the development of the gonads, the maximum weight being found at the time of rapid increase in size and development of these organs.

The lymph nodes undergo definite changes with age. Quantitative studies are few. The nodes of old rabbits (3½ years) have been said to have only about half the weight of those of animals 5 months old, when the maximum degree of lymph node development is present. The view is generally held that nodes in young domestic animals are larger than in old ones, although re-examination of this question might be made with profit.

Human lymph nodes show a decrease in amount of cortical tisue after puberty. Changes are more marked in superficial nodes, such as the inguinal, than in deep nodes, such as the deep cervical. Atrophy of the lymphoreticular tissue occurs but the volume of the node generally is retained through replacement by adipose or connective tissue, depending on the state of nutrition.

In the rat also, atrophy of lymphoreticular tissue is marked in many of the nodes and large, lymph-filled spaces are seen.

In man and other mammals the reaction centers of the nodules tend to disappear, nodular structure to become poorly defined, and distinction between cortex and medulla lost with advancing age. Definite changes in the individual cell types are seen in the rat, with an increase of active macrophages and of plasma cells.

The spleen shows a maximum percentage of follicular (lymphatic) tissue at 16 to 20 years in man and then a slow decrease seeming to continue to the most advanced age. Reaction centers are best developed at 1 to 10 years.

Similar decrease of splenic lymphatic tissue is seen in the rat. The red pulp undergoes a change from a predominantly compact, reticular character to a predominantly sinusoidal character and there are interesting qualitative changes in the cell types.

The varied changes seen in the different lymphatic organs undoubtedly are reflections of important changes in the economy of the organism as a whole. They are less susceptible to ready explanation than are changes in many of the other structures, such as the nervous, cardiovascular and skeletal organs, perhaps because the functions of lymphatic tissue itself are more difficult of explanation and rest upon cellular reactions and phenomena which we are only beginning to understand at the present time.

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THE RESPIRATORY SYSTEM IN THE AGED

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INTRODUCTION

The investigation of the biology of ageing after many centuries of neglect has been shaken free of its inertia and appears, ever so slightly, to gain in momentum. Under the impetus of a population in which the numbers and relative proportions of aged persons is rapidly increasing, the need for a concerted attack on the various aspects of the involutionary process becomes urgent. Needless to say, only the bare surface has been scratched.

While many writers in the past have debated whether ageing is essentially a genetic or environmental problem, it is evident that both play a role in the ageing process. Studies involving the morphology, physiology and biochemistry of ageing point to a primary genetic factor. However, in slowly advancing senescence, it becomes impossible to sharply delineate those factors due to the ageing process per se from those due to environmental accidents. From a structural point of view, the anatomist and pathologist is constantly striving with little success to distinguish between changes due to physiologic ageing as opposed to those deteriorations produced by an unfavorable environment. Tissue changes in the aged must for the most part represent a composite of genetic and environmental factors. This admixture of causal agents becomes even stronger when functional changes due to the ageing process are considered.

The respiratory system in general and the lung in particular possesses an organ type physiologic time clock which governs the day to day inexorable alterations of senescence. Upon this base is engraved the countless insults of a hostile environment.

The Upper Respiratory Tract

The nose

The typical weasened face of old age reflects in large measure changes in the appearance of the external nose. With the loss of teeth and the consequent absorption of the alveolar processes, the chin must be raised to a higher level in closing the mouth. The body of the mandible shifts forward with an increased obliquity to the angle of the ramus. Goldstein (1) in describing the changes in facial dimensions remarked that all lengths except the nose decrease appreciably primarily as a result of the loss of teeth. The rise in nasal index noted in old age is due to an increase in width, with the alae in many instances becoming somewhat bulbous. Basilevich (2) in his observations on a group of twelve centenarians reported a similar atrophy of the alveolar process and lower jaw even when the teeth were well preserved.

The external appearance of the nose suffers from similar changes which take place in skin and connective tissue elsewhere. Since the nose is composed largely of connective tissue and its components, the skin becomes wrinkled because of a loss of elasticity in the underlying dermal connective tissue. Dryness, with increase in the size of the pores and coarseness of skin texture is a reflection of the atrophies and involutions occurring in the sebaceous glands.

Changes in the color of the external nose are more apt to reflect certain environmental and nutritional factors making for alterations in vascularity than to represent any phenomena of the ageing process. Certainly, variations in color are as common in the adult as in old age. In addition, the bulbous deformity of the tip of the nose, rhinophyma, while seldom seen before middle age is nevertheless the end result of a chronic acne rosacea and as such is not representative of senescence.

While the extent of our knowledge concerning changes in the shape, form and texture of the external nose as modified by age is gleaned from the observations and factual reporting of many investigators, in keeping with physiognomy generally, the influence of heredity is of major importance. The tendency towards atrophy or hypertrophy in senescence will be determined and modified by certain familial and racial characteristics of the individual.

The membranes of the nose and upper respiratory tract in general are more exposed to the insults of the environment than any other organ or tissue. Functioning as the initial portion of a conduit, large quantities of air with all its contained irritants and foreign particles are passed over its surface continuously during the process of pulmonary ventilation. In ad-

dition, the nose must condition this air to the proper temperature and humidity, must filter out much of the particulate material including bacteria, *and function as the end organ for the perception of smell*. To attempt any separation would be futile since changes as a concomitant of age alone are few "and result largely from simple atrophies of the mucosa, the glands, and the muscles, similar to those found elsewhere in the body" (3).

Those factors in the environment which are for the most part inescapable and play an important role in accelerating the general atrophy associated with ageing include noxious smokes and dusts in the inhaled air, excessive smoking, the ubiquitous "common cold", and over-heated, excessively dry housing. The *inhalation of such air provokes marked dryness of the nasal* mucosa with chronic irritation of the throat and accessory sinuses as well. Secretions become viscid and dry interfering with ciliary activity. The end result is atrophy of the mucous membrane. The turbinates become pale, dry and crusted with occasional patches of squamous epithelial metaplasia. Hollender (4) in a histopathologic study reported a decrease in the normal accumulation of lymphatic tissue in the subepithelial layer. This was replaced largely by connective tissue which was more abundant than usual and showed frequent deposition of hyaline. This involution of the subepithelial lymphatic tissue with proliferation and hyalinization of the connective tissue results in a compression and atrophy of the glands. The atrophy of the nasal mucosa and glands in senescence may resemble superficially the picture of atrophic rhinitis which is similarly characterized by fibrosis of the mucosa. The fibrosis in atrophic rhinitis occurs as a firm scar following an inflammatory process usually chronic sinusitis and is not age-linked. A hormonal disturbance has been implicated. Epithelial metaplasia from a ciliated columnar to the squamous type membrane is accompanied by crusting and decomposition. In ageing, the fibrosis is due to degenerative changes involving an involution in the lymphoid tissue with only scattered areas of glandular destruction (7).

Schaeffer's (5) description that the highly vascular cavernous tissue of the nasal fossae is at its height during sexual life and frequent reports of this membrane participating in vicarious menstruation in the female would suggest that the steroid hormones of the ovary exert an important influence. Rosenwasser (6) agrees with Schaeffer in that an increase in fibrous connective tissue involves the vessels causing some obliteration of the vascular spaces. Hollender, however, reported that the effect of ageing on the nasal corpus cavernosum may present a hypertrophy in that its blood spaces become increased in number at the expense of the interstitial and subepithelial tissues of the mucosa.

Little is known concerning specific changes in the cartilages and bones of the nose. Rosenwasser (6) reports that the turbinate bones undergo

atrophy and cites the history of an 85 year old female who was found to have a papyraceous transformation of the bony wall of the maxillary sinus.

With the passage of time, some deterioration of the special senses becomes evident with partial or complete loss of the sense of smell. Aberrations of the sense of smell, parosmia, may be a source of great annoyance to the elderly individual. While the causative factor may be the end result of repeated infections in which the olfactory endings are injured or destroyed, senile atrophy of the olfactory portion of the nasal mucosa may be implicated. Smith (8) in a pathological study of 205 human olfactory bulbs noticed a progressive loss of olfactory fibers associated with ageing. No sex difference in loss of fibers was observed. A tabulation of the average per cent loss of ganglion cells for fifteen year periods is reproduced:

Age (yrs)	Average loss in per cent
0–15	8
16–30	20
31–45	33
46–60	57
61–75	68
76–91	73

(From Smith, C. G. J. Compar. Neur 77, 589, 1942.)

Smith ascribes the tendency of the olfactory nerve fibers to atrophy as possibly due to the exposed position of the ganglion cells located in the epithelial lining of the roof of the nose. Factors involved therefore, would be 1) age and 2) inflammatory or irritating reactions.

The senescent degenerations of the nasal mucosa consisting for the most part in dehydration and waste of tissue may irreversibly affect the ciliary activity of the epithelial cells in the nose and paranasal sinuses. Bollenger (9) has shown that ciliary beat is rapidly impaired by drying. In addition, ciliary streaming is slowed down or impaired if the layer of mucus becomes too thick and viscid as a result of this drying (10). Consequently, the bacteria and viruses enmeshed in the overlying blanket of mucus which would ordinarily be removed by ciliary action may remain in contact with the nasal epithelium long enough to penetrate the mucosa and produce infection. There is no information on whether the secretion of lysozyme or the pH of the nasal mucosa is altered as a result of the ageing process (11).

While sinusitis is a common ailment in the aged and is responsible for a multiplicity of symptoms, there are no diseases of the sinuses peculiar to senescence. Proetz (11) confirms Nascher's statement that for the most part nasal and sinus disease becomes milder year after year due to an improvement in ventilation brought about by increasing atrophy and fibrosis of the mucous membrane. Many conditions believed to be a sinusitis are in

reality a form of chronic vasomotor rhinitis. Although the allergic form of rhinitis is more common in the first three decades of life, Ashoff (13) mentions the increased formation of nasal polyps in early senescence which he believes is partially endocrine in character. Taub (14) confirmed this by reporting a group of cases occurring in women past the menopause who were benefitted by hormone therapy. He felt, furthermore, that vasomotor rhinitis was present in a small but well defined group of elderly subjects due to some form of physical allergy such as a hypersensitivity to cold, heat or light.

Although malignant and nonmalignant tumors of the nose occur most *frequently between the ages of fifty and seventy, like tumors elsewhere,* there is no evidence that they are part of the ageing process. The squamous cell type of epidermoid carcinoma is the most common form in the aged. Probably as a result of chronic irritation, metaplasia of the columnar epithelium to the stratified squamous type precedes the malignant transformation.

The pharynx

Muscular atrophy involving the constrictors of the pharynx and palate and resulting in the waste of the faucial pillors and walls has been described by Thewlis (15) who discussed the changes in the musculo-skeletal system with age. Loss of elasticity and resiliency occur with the general dehydration and atrophies of ageing producing functional impairments.

The form and position of the nasopharynx is altered. Lion (16) compared the sagittal cross sections of the nasopharynx of a child with that of an adult. During childhood, the nasopharynx lies at the same level as the posterior segment of the inferior turbinate. Owing to variations in growth of the nasal cavity and face, the nasopharynx becomes stretched as high as the middle turbinate. At the same time, the pharyngeal opening of the eustachian tube rises from the level of the hard palate to the level of the inferior turbinate bone.

It would appear that changes in the mucosa of the nasopharynx would be similar to the senescent degenerations of the nasal cavity. A dry, atrophic pharyngitis is common in the aged. Predisposing factors such as repeated infections of the nasopharynx and the exposure to an overheated environment with low humidity appears to inhibit the orderly ciliary activity with a marked impairment in the capacity for self-cleansing (17). Scanty mucus secretion diminishes the protective action of the lysozymes (18).

In keeping with lymphoid tissue in general, the tonsillar masses of the pharynx apparently reach their maximum development in childhood and decrease in size after puberty. Halasz (19) considers the tonsil from an endocrine point of view with its function completed at puberty to be suc-

ceeded by involutionary changes. Keleman (20, 21) while he agrees that there is a steady decline in the size of the tonsil with advancing age, noted a temporary increase in volume during the sixth decade. The diminution in size was somewhat accelerated between the seventh and ninth decades and while complete absence was rare several individuals in the ninth decade had a total absence of tissue in the fossae. The capsule remains well outlined but the cells decrease in number until its final disappearance with the parenchyma maintaining its function of lymphocytic development. The tonsillar tissue behaves like other lymph node structures in that at any period, the stimulus of local inflammation may cause proliferation and a partial reversion so the childhood state. For this reason "the tonsils rarely reveal the age of their bearer". Denz (22) in his excellent review of the age changes in lymph nodes, believes it incorrect to consider lymphoid tissue as a "structure built at puberty to last until death". It is probably undergoing constant slow change so that an infinite number of minute variations over the course of many years produces an entirely new structure.

Tonsils which have been exposed to repeated infections undergo extensive fibrosis. As atrophy progresses, the network of fibrous tissue at the mouths of the crypts prevent their free drainage harboring pathogenic organisms which could conceivably serve as a focus of infection.

In addition to serving as a portion of the conducting system for the respiratory tract, the pharynx is intimately associated with the process of deglutition. While difficulties in swallowing and aspiration of food is a problem at all age levels, the elderly appear particularly vulnerable. These accidents may vary from the acute asphyxia of a major obstruction to the airway, to the low grade chronic pneumonitis associated with protracted aspiration. Some of the factors which make this a peculiar problem of the aged have already been mentioned; the general muscular atrophy of the constrictors of the pharynx and palate, and the drying out of the mucous membranes associated with impaired ciliary activity. Furthermore, there is evidence that salivary secretions are diminished in ageing (23). Andrew (24) observed marked degenerative changes in the parotid glands of senescent rats. This would make for insufficient lubrication of the bolus. Reduced sensitivity of the mucosa and an impaired reflex mechanism contribute to the more frequent occurrence of accidents during the swallowing act in the aged.

The larynx

The larynx appears as a more prominent structure in senescence. This is due in part to the atrophy in the surrounding muscles of the neck and to the increased anterior bowing of the cervical spine which throws the larynx and trachea into greater relief. The folds of loose skin heighten the

scrawny effect thus produced. Ashoff (13) noted a lowering of the position of the larynx. From a level of the fourth cervical vertebra in the newborn, it may descend to the second or third thoracic vertebra after sixty. The cross sectional diameter of the larynx and trachea appears to widen with age and is more marked in the male, which Ashoff attributes to the increased use of the voice in this sex.

The cartilages begin to show fibrillar changes of the ground substance in early adulthood. Ossification takes place during adult life. The ossification centers appear in the thyroid, cricoid and the basal parts of the arytenoid cartilages. The epiglottis becomes fibrosed (12). Ashoff mentions the frequent occurrence of calcification in the laryngeal and tracheal cartilages as opposed to the rarity of this occurrence in the bronchi. Rolliston (25) describes this calcification as a pathological process and not part of ageing per se. The deposition of calcium salts appears to take place with greater frequency in cartilage which has acquired a yellowish tint due to lipid accumulation. This type of change would closely resemble the arteriosclerotic process.

Atrophy of the laryngeal mucosa with occasional islets of metaplasia of the ciliated epithelium to a stratified squamous type has been described. Nascher (12) discussed the similarities of chronic laryngitis to bronchitis. He points out that this is a true senile disease depending upon the presence of an atrophic mucous membrane subject to irritation. Symptoms consisted of weakness of voice without hoarseness or aphasia, a feeling of excessive dryness of the throat with occasional attacks of spasmodic cough.

Nonmalignant tumors of the larynx are most frequent in maturity at a time when "use and abuse" of the voice are greatest. Of the malignancies, Proetz (3) quotes the data of Figi and New who reported 84 per cent of 380 cases occurring between the ages of forty and seventy with 9 per cent in patients between seventy and eighty. The preponderance in males of the order of ten to one is striking.

The general muscular atrophy of the pharynx and larynx which takes place in old age may play a significant role in the voice changes of senescence. Bach et al. (26) describes definite degenerative changes in the laryngeal muscles of five old persons consisting of 1) fatty degeneration of the cricothyroid, 2) increase in the loose areolar connective tissue and of the nuclei of the sarcolemma, 3) absence of cross striations in certain sections with "spindle-like swellings and discoid decay", and 4) definite hyperemia of the blood capillaries with occasional edema of the connective tissue. In all five cases, the abductor muscles of the larynx were more affected than the adductors. These changes were ascribed to the vascular disturbances accompanying senescence with a diminution in nutrition to the affected

muscles. After reviewing the literature, Bach and his associates felt that these muscle atrophies were sufficient to explain the senile voice. Certainly, the failure to maintain the normal tonus of the cords would result in changes in pitch rendering the voice monotonous, flat and occasionally shrill. However, as Macklin and Macklin (27) have pointed out, the high pitched quavering voice characteristic of the aged is probably the resultant of a number of mechanisms involving deteriorations in fibro-elastic tissue, neuromuscular coordination and the blood supply.

The thorax

Respiration in its broadest sense refers to the gaseous interchange between an organism and its environment. The exchange of oxygen and carbon dioxide between the pulmonary capillary bed and the air in the lungs involves, principally, certain mechanical and physicochemical mechanisms which depend on the integrity of the entire pulmonary complex consisting of the thoracic cage and its supporting elements, and the bronchopulmonary structure. Two major systems serve the respiratory requirements of the tissues; the lungs, with a ventilatory apparatus and a large breathing surface for contact between air and blood; the circulation, with its capacity for gas transport to and from the tissues. In the performance of respiration, the pulmonary and circulatory apparatus form an integrated system (28).

It is apparent that any structural change in the thorax accompanying the ageing process would conceivably alter respiratory function. And yet, it is surprising how well the pulmonary complex continues to serve the individual in extreme age Here, perhaps more than elsewhere in the body, the numerous minute impacts of environmental injuries mingle with the subtle changes due to passage of time so that in the final analysis, true physiologic change cannot be distinguished from the pathological deteriorations.

The aged person is typically pictured as assuming a stooped, bent-over posture. This position has been attributed to a weakening and relaxation of the back musculature together with changes in the vertebral column. As early as the fiftieth year, Vischer (29) finds a measurable diminution in body stature due to alterations in the intervertebral cartilages which grow thinner, smaller and drier. The constant muscular effort necessary to the maintenance of the erect posture weakens as a result of degenerations in the voluntary muscles. Rolleston (25) emphasizes changes in the skeletal muscles consisting of loss of cross striations, deposition of large globules of fat amongst the fibers, and the increase in brown pigment found in the immediate vicinity of the muscle nuclei.

In considering the bony and cartilaginous elements of the thoracic cage,

much emphasis has been placed on changes occurring in the intervertebral cartilaginous discs of the vertebral column. Warthin (30) described the typical senile thorax as having a short, sharply curved spinal column with contracted and thinned intervertebral discs. The thorax was barrel shaped with a wide epigastric angle. Kountz and Alexander (31) attribute senile emphysema to postural changes of old age consisting for the most part of a kyphosis which develops secondary to intervertebral disc changes.

Nascher (12) claimed that the erect posture caused the discs to become compressed with the greater stress occurring anteriorly in the dorsal spine and resulting in a spread of the posterior borders. This would account for *the increased curvature in this region with the production of a kyphotic* deformity. Coventry, Ghormley and Kernohan (32) in an excellent study of the microscopic anatomy and pathology of the intervertebral disc review the changes occurring at various decades. In the sixth decade, thinning of the disc was apparent in three of the twenty-two specimens. Fibrillation of the ground substance and calcifications in the cartilaginous plate were common. The cartilage cells tended to lose their distinct outline and nuclei became pyknotic. In the seventh decade, degeneration was extensive in thirteen of the twenty-seven cases. Longitudinal bands of fibrous tissue and calcium plaques were evident. In places, the cartilage was replaced by bone. Tears were frequent with the annulus showing areas of necrosis and hyalinization. These changes were attributed to the excessive wear and tear to which the spinal column is inevitably exposed. In addition, senescent changes in the vascular supply would aggravate the deteriorations produced by day to day trauma.

The ribs in order to accommodate themselves to the changed articular relations with the spine in back and the ossified costal cartilages in front became flattened at the sides. These structural changes together with the lessened resiliency of the ribs themselves make for the typical senile chest which is longer anteriorly, foreshortened posteriorly, and flattened at the sides.

Considerable differences of opinion exist in the literature concerning age changes in the costal cartilages. Rolleston (25) considers calcification of the costal cartilages, as with the laryngeal, a pathologic process. He records that amongst ten recorded necropsies on centenarians, the costal cartilages were calcified in only two. Basilevich (2) supports this view since he found no evidence of ossification or calcification in his group of twelve centenarians. Nascher (12), on the other hand, regards ossification as a common finding in the aged. Both Vischer (28) and Thewlis (15) state that the costal cartilages suffer a loss of elasticity and become calcified. The cartilages become brittle and easily fractured. The resulting rigidity

of the thorax would in part account for the diminution in lung capacity which may be noted as early as the fifth decade. Taylor and Schwartz (33) in a roentgen study of 125 men over fifty years of age found evidence of calcification of the costal cartilages in 93 members of this group.

Haas (34) in a morphologic and chemical analysis of human costal cartilage describes an increase in the amount of chondroitin-sulfuric acid in proportion to the increase in the ratio of matrix to cells from infancy to the 4th decade. During this period the cartilage is white, homogeneous, translucent and resilient. Through the 4th and 5th decades, the axial region of the cartilage begins to show yellow pigmentation and becomes more opaque. Diffuse areas of calcification with patches of linear fibrillary striations become recognizable and resiliency is decreased. In later life, despite further increase in the ratio of matrix to cells, the amount of polysaccharide decreases. In the 8th decade, the quantity of chondroitin-sulfuric acid has been reduced to less than half the value in maturity. Calcium deposits become prominent and islands of tissue disintegration, osteoid matrix and bone are often present. The yellow pigment which is neither lipid nor iron contributes a brown tinge to the cartilage.

Senescent changes in the synovial membrane, capsular ligaments and supporting tissues of the joints may be expected in the thoracic cage, as elsewhere in the body. In the upper costal respiration, the manner of articulation of the upper six ribs with the vertebrae results in an upward and forward movement of the anterior chest in inspiration, with relatively little lateral expansion of the ribs. On the other hand, when the ribs enclosing the lower half of the chest are raised in inspiration, there is a wide lateral flare (35). With a diminution in mobility of the joints between the ribs and vertebrae posteriorly and the sternum anteriorly, the movements described would be impaired. Chest expansion would be interfered with and the mechanics of respiration handicapped.

The superficial coverings of the thorax including the skin, connective tissue and muscles are altered with the passage of time. In the female, the breasts undergo atrophy, become wasted and pendulous. The skin becomes wrinkled because of the loss of elasticity of the underlying dermal connective tissue. When stretched over the bony framework of the ribs and clavicles, it may assume a parchment-like quality. Ward (36) in discussing the connective tissue changes with ageing mentions the apparent reduction in ground substance noted by Bensley. The ageing of connective tissue appears to involve a process of dehydration which may actually represent an increase in the ratio of the cells to the extracellular fluid. Lowry and Hastings quoted by Ward, found a rise in the extracellular fluid which may represent a relative increase because of atrophy and decrease in the cellular

compartment. They conclude that "actual evidence for change in the composition of the cytoplasm remaining functionally active in the very old is still lacking".

Thewlis (15) describes similar changes due to waste and dehydration taking place in the muscles of the chest wall. At times, there may be an actual proliferation of connective tissue fibers through the muscle bundles. There occurs a resulting loss of elasticity and resiliency with impairment of function. Nascher (12) finds the greatest waste occurring in the intercostal muscles and diaphragm which he believes is related to their being the most actively employed muscles excepting myocardium. As a consequence of this muscle waste, the intercostal spaces and the supraclavicular and infraclavicular fossae appear more prominent. In Warthin's (30) description of the fully developed picture of old age, the interspaces are said to be obliterated. But this may represent a pathological alteration depending upon the kyphotic deformity of the thoracic spine.

From the foregoing, it is difficult to judge what alterations in thoracic configuration would most ideally represent the depreciations of time alone. Those of us who have worked with old persons in hospitals and institutions for the aged have been struck on more than one occasion by the upright appearance, squared shoulders and straight backs of people in the seventh, eighth and ninth decades of life. The most common alteration described in the literature is one of kyphosis. In Basilevich's (2) study, most of the centenarians exhibited a marked kyphosis but the lungs appeared healthy on x-ray. Both Thewlis (15) and Rolleston (25) describe similar changes with the latter emphasizing the pathologic nature of the vertebral bowing. Furthermore, he asserts that calcification and ossification of the anterior common spinous ligament is a common feature of this deformity. Nascher (12) describes the typical senile chest as resembling the rachitic thorax. He further states that the senile kyphotic chest is more common in men than women. Macklin and Macklin (27) challenge this statement and refer to Albright's studies on osteoporosis of the spine and pelvis occurring in women past the menopause which could conceivably favor compression of the vertebra with bowing.

In the "barrel-chest" configuration described by Warthin (30), the antero-posterior diameter of the chest approaches and may even exceed the transverse diameter exhibiting a reversion to the infantile state. For the most part, this type of chest has been associated with pulmonary emphysema although Cabat (37) could not find any such correlation. This subject will be pursued further in discussing emphysema.

There are no adequate statistical studies of the normally ageing thorax as depicted by roentgenologic methods. It is evident that large numbers of chest films from institutions for the aged and from the mass surveys of many segments of the population within recent years should provide in-

teresting material for such an "arbeit". Taylor and Schwartz (33) in their study on 125 men over fifty years of age reported observations which were for the most part pathologic in character rather than a pure age change. In only twenty-nine members of this group, roentgen examination revealed no "positive findings". For the rest; interstitial changes suggesting bronchiectasis were present in thirty-six; thickened pleura in twelve (two with pleural calcification); senile emphysema in ten and a tuberculous process in ten, none of whom had symptoms. Cardiac hypertrophy was found in thirty-four persons and aortic dilatation in fourteen associated with clinical hypertension. Eight members of this series presented calcific deposits in the aortic arch. The extent of costal cartilage calcification has been mentioned. Polgar (38) observed that the frequency, as seen on x-ray, of the horizontal bipartition of the thoracic cage increased with age. The greatest depth of this lateral thoracic furrow, two centimeters, was present in old people suffering from emphysema.

In reviewing the literature on the configuration of the ageing thorax, the three types described appear to predominate The kyphotic thin chested thorax is in all likelihood the resultant of pathologic deteriorations in the vertebral column, weakness of the supporting muscles and the constant pull of gravity. The barrel-chested thorax is not infrequently seen in younger people. Moreover, many persons of advanced age do not present this deformity. The frequent association of enlargement of the antero-posterior diameter of the chest with obstructive emphysema raises the suspicion that similar forces such as loss of lung elasticity would, in part, be responsible for the fixation of the thorax in the inspiratory phase. Macklin and Macklin (27) have raised the question of a diminished sensitivity in the receptors and afferent pathways initiating the act of expiration as maintaining the chest in the inspiratory state with a secondary deterioration in pulmonary elasticity. My observations on elderly people with and without chest disease leads me to feel that the effects of ageing alone are not manifested by these deformities. While the thorax appears smaller, shorter and lighter, the spine is straight with no increase in the antero-posterior diameter. The superficial coverings may be wasted making for greater prominency of the bony structures, and deepening the intercostal spaces. Perhaps, as with changes in facial physiognomy, genetic and racial factors play an important role in determining the configuration of the ageing thorax.

Lower Respiratory Tract

The trachea and bronchi

old age. Merkel (40) places it as low as the seventh thoracic vertebra in the aged. This is supported by Brock's (41) recent work. Associated with this descent in the bifurcation of the trachea, the angle at which the two main bronchi are given off varies with age. According to Nascher (12), there is a similar recession of the lung itself in which the upper lobe of the left lung sinks and falls forward of the lower lobe, while in the right lung the middle lobe sinks and falls in front of the lower lobe. As a consequence of these shifts, the apices descend thereby causing an alteration in the percussion note of the supraclavicular fossa.

Calcifications occurring in the tracheal cartilage are described by Thewlis (15) while Nascher (12) intimates that rigidity of the trachea and upper portion of the bronchial tree may result from calcareous incrustation of the cartilages. Ashoff (13) finds calcification in the trachea in a large number of his series but comments on its rarity in the bronchi. He mentions a "saber type" *appearance of the trachea frequently seen in the presence of thyroid* struma. In the aged, these changes are apparent in the absence of thyroid enlargements and he hypothesizes that an increase in blood pressure within the carotid arteries may cause identation of the trachea.

While Ashoff (13) refers to a widening of the trachea with increasing age, there is little evidence that the respiratory airway of the upper passages is altered in senescence. Nascher (12) finds the calibers of many of the smaller bronchioles diminished in size with occasional obliteration of the lumen. Contrary to the theoretical assumption of an enormous increase in the cross-sectional diameter of the pulmonary air passages, Hilding (42) found an increase in volumetric capacity of only 50 to 100 per cent over that in the trachea. Barring the pathologic states such as emphysema with its increase in residual air, the volumetric capacities do not appear to change significantly with ageing. This would have an important bearing on the relationship of tidal air to dead space.

The lung

Senescence, as a pure physiologic expression of old age, involving processes of involution and atrophy uncomplicated by pathologic deteriorations is conceded as being extremely rare. The lungs, in their daily exchange of enormous amounts of air with the external environment, are more exposed to the adverse influences of such an environment and hence show the accumulation of pathologic insults in greater degree perhaps than any other organ of the body. It is extremely doubtful if the pathologist in his necropsy material has an opportunity to observe age changes in the lungs per se. Yet, based on reports in the literature, it would be interesting to speculate on what such changes might be in a normally ageing lung.

Both Nascher (12) and Rolleston (25) indicate that the primary de-

generation is one of atrophy resulting in a diminution in size and weight. Korenchevsky (43) found a relative hypoplasia of the organs in ageing rats. Because of this, hypoplasia must be considered a feature of ageing but he wondered if it represented a physiological adjustment to the slowing of growth, or perhaps, a latent wear and tear of living tissue in general whose end point was true senile atrophy. Krusen and Leden (44) agree with the majority of investigators that the essential change in senescent atrophy is probably one of dehydration and tissue waste which is either not repaired at all or replaced by tissue of a lower order of differentiation. It is extremely difficult to compare data for the weight of the lungs since the amount of blood contained varies widely. The pulmonary vascular bed in its capacity as a blood depot may hold large amounts of blood. In the normal resting state, the lungs are said to contain between 300 and 500 cc. of blood. Reichinstein (45) gives the average weight of the right lung as 570 grams in the age group 65 to 85 years. This decreases to 438 grams between 85 to 90 years. For the left lung, the corresponding figures are 430 grams at 65 to 85 years and 350 grams at 85 to 90 years. In comparing the sexes, the decrease in weight was not as striking in the female.

The color of the senile lung has been described by Nascher (12) and Thewlis (15) as grayish with black areas and lines over its surface and throughout the tissue. This is contrasted to the characteristic yellowish pink appearance of the normal lung in the child and young adult. Color change, however, is dependent in large measure upon inhaled carbon and other pigmented substances which accumulating over the course of time impart a grayish or blackish tinge to the tissue. The increase in air pollution from industrial smokes and vapors, the rising incidence of tobacco consumption in the general population, and the exhaust wastes of our mechanized civilization offers a reasonable explanation for the anthracotic-like appearance of the aged lung. Also, the degree of congestion of the lung must be considered. At death, blood tends to settle towards the posterior aspect or most dependent portion of the lung. Therefore, the lung when observed at autopsy may appear pale and anemic on its anterior surfaces and dark over the posterior aspect. The effect of pathologic processes such as pneumonia, tuberculosis and pneumoconiosis while altering the color of the lung cannot be considered as an age change.

There are few reports on the condition of the pleural surfaces. Nascher (12) states that the visceral pleura becomes thin, opaque, dry and lusterless. In advanced age, the layers are generally adherent to each other with the parietal pleura coherent in places to the chest wall. Thewlis (15) mentions an unevenness of the lung surfaces. In the series reported by Taylor and Schwartz (33), there was x-ray evidence of thickened pleura in twelve of 125 subjects, two of whom exhibited pleural calcification. It must be

assumed that adhesive changes in the pleura represents an inflammatory process and thus a pathologic variation rather than one due to senescent degeneration.

It is frequently noted at the autopsy table that the lungs of elderly subjects do not exhibit the prompt collapse found in the young. Retractility is sluggish and deflation is incomplete. Nascher (12) finds that the aged lung has a more "elastic feel" but with diminished crepitation. Pathologists are inclined to accept a moderate degree of alveolar emphysema particularly of the peripheral portions and expanding edges as a normal finding in senescence. The retained air in these segments could account for the spongy feeling described by Nascher and would have no relationship to alterations in tissue elasticity. In advanced old age, Thewlis (15) reports that the lungs lie near the vertebral column. The shape may be further altered by changes already noted in the configuration of the thoracic cage.

The pulmonary complex

While it is not the intention of the author to give a complete detailed description of the broncho-pulmonary tree, a knowledge of basic pulmonary structure is essential to the analysis of senescent change. For a comprehensive account of the anatomy and histology of the lung, the reader is referred to the excellent monograph by Miller (46) in which he summarizes the work of other investigators and the results of his own lifetime of study and the numerous papers of Macklin (47, 48, 49, 50, 51, 52).

Grossly, each lung consists essentially of two lobes with a deep fissure extending to the root of the lung between them. The right middle lobe is actually a part of the upper lobe. This fissure divides each lung into roughly two equal parts. Each lobe of the lung is further divided into a number of lobules which are wedge-shaped masses of tissue separated from adjacent lobules by bands of connective tissue. The lobular bronchiole enters this segment of the lung at its apex. Within recent years, anatomists and thoracic surgeons, in an effort to correlate pathologic physiology with lung structure, have made an intensive study of the segmental anatomy of the lung. The reader is referred to the papers of Foster-Carter (53), Walker (54), Churchill (55) and Temple and Evans (56).

The trachea is described by Miller (46) as consisting of a framework of cartilaginous crescents, 16 to 20 in number, interconnected by a dense layer of connective [illegible]

smaller bronchi contain scattered plates of cartilage The cartilage disappears [illegible] the level of bronchi with a 0.6 mm. diameter. A strong muscular network forming

a lattice-work about the circumference of the bronchi and described by Miller as a geodesic pattern supplies tensile strength and support. Because of this basic structure, the trachea and bronchi are not rigid but capable of alterations in internal diameter as well as a certain degree of mobility. Elastic fibers like those in the trachea run lengthwise along the bronchi and bronchioles between the muscular layer and the mucosa. At the distal end of the alveolar duct, the muscle forms a sphincter about the openings leading into the atria. Distal to the sphincters, no muscle is found. Richards (28) points out an interesting relationship between the size of the muscle bundles in the larger as compared to the smaller bronchi The muscle bundles would appear to be five times as strong in the bronchiolar division as in the larger bronchus. The mode of division of the bronchi is monopodial for the main series and a mixed dichotomy and monopody for the smaller bronchi

Macklin and Macklin (27) recognize two divisions in the functional anatomy of the tracheobronchial tree. The conducting portion of the complex whose main function is gas transport has been described above The respiratory part of the airway is concerned with gas exchange and consists of the respiratory bronchiole, alveolar duct and alveolar sac The walls of the alveolar sac are evaginated into the many terminal air cells. These outpouchings or alveoli occupy practically the entire wall forming a sponge-like system of air cells. The alveoli themselves are supported by networks of elastic fibers.

The epithelial lining of the conducting portion of the airway is of the ciliated columnar type becoming cuboidal in the bronchioles. The cilia are approximately 7 0 μ in length and 0 3 μ in diameter. Bollenger (9) found an average of 8 5 cilia to the surface of a cell Hilding (42) estimated that the cross-sectional area of ciliated epithelium of the smaller bronchioles increased approximately 25,000 times over that in the upper respiratory tract. The ciliary mechanism is largely responsible for the removal of secretions under normal conditions and appears to be free of neurogenic control. There is considerable debate as to whether the respiratory epithelium extends intact over the alveolar walls as a continuous membrane (Miller (46), and Sante (57)) of thin flattened squames which are closely applied to the alveolar walls. Loosli (58), Macklin (59) and Ham and Baldwin (60) believe that the epithelial lining becomes discontinuous Loosli claims that the cells do not flatten but degenerate during the later stages of intrauterine life so that the pulmonary capillaries, in places, are covered only by ground substance and a reticulum of the mesenchymal tissue Some isolated epithelial cells which are low and nonciliated occur singly or in small groups Clara (61) has termed these cells "epicytes"

Interesting speculation has been raised as to whether the so-called pores of Cohn exist in the normal lung or result from pathologic processes Miller (46) feels that the alveolar pores develop in disease states through the shedding of the epithelial lining. Van Allen et al. (62) presented evidence in dogs for the existence of inter-alveolar communications Macklin (51) attributes the origin of the alveolar pores to a gradual atrophy of the ground substance. Moreover, they appeared more evident at older ages and were larger and more numerous in the thin borders, subpleural layer and apical regions He mentions the etiologic similarity to the fenestrae of early emphysema Sante (57) feels that the healthy alveolar membrane will permit air to pass directly between adjacent lobules through the small openings or "pores". This would help to equalize the pressures in adjacent cells. Segmental collapse would be possible if edema or infiltration caused a loss in air permeability of the alveolar wall by virtue of having blocked these pores.

The mucin secreting goblet cells and the bronchial glands form an integral part

of the epithelium whose main function is providing and maintaining the necessary elements of the mucous "blanket" As such, their integrity is vitally concerned in the self-cleansing properties of the normal lung.

The interstitial connective tissue forms a structural framework composed of a fibrous stroma and a complex elastic reticulum. In the hilar region, the connective tissue is bulky offering passage for the bronchi, blood and lymph vessels. The fibrous tissue about the vessels arranges itself into tough perivascular sheaths extending from the hilum to the terminal air cells and back into the mediastinal space as a continuous sheet. This has been evidenced by the pathway of air in pathologic states such as interstitial enphysema *From the respiratory bronchiole, the fibrous* tissue stroma appears to fray out as it is distributed to the terminal portions of the primary lobule. According to Sante (57), the alveolar lining is held in close relationship to its surrounding capillaries and to each other by this fibrous tissue stroma. While primarily a supporting structure, it is readily adaptable to the various movements and changes in shape required for adequate lung ventilation.

Functionally, the elastic tissue constitutes an important element in the respiratory tract, and is present in proportionately large amount. Miller (46) found a complex web-like pattern of elastic tissue permeating the entire lung In the conducting portion, it is made up of fasciculi coursing between the muscle layer and the epithelium Many of these fibers also run circularly or obliquely In the respiratory portion of the lung, the elastic fibers became more delicate and wreath-like. Together with strands of smooth muscle and fibrous tissue, they assume a spiral course curving *about the openings of the alveolar ducts and sacs and passing into the walls of the* alveoli This system together with the smooth muscle is intimately concerned with the inspiratory and deflationary movements of the lung which will be discussed in greater detail in the section on pulmonary function.

Ham and Baldwin (60) in their histological study of the development of the lung describe two types of mesenchyme, one, relatively cellular and closely applied to the endodermal tree, "clothing and capping" its many branches; while the other, relatively non-cellular, fills in the remaining space. The latter differentiates into the extrabronchial connective tissue which may be subdivided into pleural, perivascular, peribronchial, interlobular and hilar. It is composed for the most part of loose fibrous tissue containing strands of smooth muscle and elastic tissue fibers. The whole forms a continuous network which contains the lung in a sort of sac.

The vascular structure of the lung is unique in many respects It is exposed to the *same air pressure and form change as the pulmonary airway itself.* Therefore, mobility and elastic recoil would be at a premium as compared to the systemic circuit. Under normal circumstances, the lesser circulation is exposed to an intravascular pressure approximately one-fifth that of the peripheral arterial system The blood supply to the lung arises from two sources: the bronchial, as a division of the systemic

[illegible]

describes the bronchial and pulmonary circulations as anastomosing at the capillary level. Marchand et al. (63) disagree with this view. They find that arterial anas*tomoses* exist in normal human lungs and that an apparent increase in the number of such anastomoses takes place in disease due to the dilatation or "opening up" of

existing channels which are vitally concerned with the redistribution of blood flow within the lungs.

There is an intricate pressure relationship of the capillary bed to the alveolar structure (57). During inspiration, the increase in the volume of the thoracic cavity is taken up by the increase in air and blood content. The blood volume in the lung may increase as much as fifty per cent. The thin-walled capillaries are capable of withstanding a certain degree of pressure from the distended alveoli and the elastic reticulum serves to limit and prevent overdistension of the alveolar structure. It is obvious that any change in interalveolar pressure will be transmitted directly to the capillary thus helping to equalize pressure changes taking place between the alveolus and the circulation. The increase in blood volume during deep inspiration may be explained by the fact that the blood capillary thus guarded against the pressure exerted by enlargement of the alveolus is subject to the increased negative pressure in the expanding thorax. During expiration, the elastic recoil squeezes out the excess blood thus producing a pump-like action; important factors in pulmonary circulation and adequate aeration since the same pressure gradients which provide for ventilation also provide for the necessary blood flow.

The lymphatic tissue of the lung has been described by Miller (64) as forming a closed system of vessels not communicating with the air spaces or the pleural cavity. An abundant supply of lymphatics exist which are subdivided into a superficial or pleural and a deep set. These communicate with each other at the hilum and pleura. The bronchial lymphatics terminate at the distal end of the alveolar ducts where they join the lymphatics of the pulmonary vein. Valves permit unidirectional flow although few valves are found within the lung itself. The amount of lymphatic tissue in the pleura is considerable but no true nodes or follicles are present. Miller states that "the quantity of lymphoid tissue increases from childhood to old age and is largely due to the irritation arising from the constant inhalation of irritating substances". In those lungs which showed most pigmentation, the lymph nodes at the hilum and the bronchopulmonary nodes were increased in size and highly pigmented. Furthermore, he remarks that in lungs from individuals sixty or more years old, there is a small node in the angle formed by the main stem bronchus and its third ventral branch. Under the age of thirty, this is rarely found. The lymphoid tissue associated with the finer branches of the bronchial tree is always increased in quantity with ageing and this is especially marked at the respiratory bronchioles and at the distal end of the alveolar ducts. Besides these distinct masses, in old age, there is a delicate layer of diffuse lymphatic tissue in the walls of the bronchi and larger bronchioles situated between the epithelium and the smooth muscle. In addition, a sheath like mass may completely surround the pulmonary arteries which one never sees under the age of thirty. Where lymphoid tissue is associated with the pulmonary veins, it is increased in quantity with ageing, and similarly, there is an increase in the lymphoid tissue of the pleura which may be deeply pigmented especially if the individual had lived in a dusty environment.

The nerve supply of the lungs is formed by branches of the vagi and the 2nd, 3rd and 4th thoracic sympathetic ganglia which make up the anterior and posterior pulmonary plexi. Branches are given off which supply certain areas of the visceral pleura and the entire bronchial tree. Fibers are given off to the main bronchi and pulmonary vessels at the hilum. Ganglia are present along the extrachondral and subchondral plexi within the bronchial walls. Afferent receptors are distributed along the epithelial lining of the bronchi as free endings while specialized flattened end organs line the atria. The lower six thoracic and phrenic nerves supply sensory

fibers to the diaphragm while motor innervation is derived from the phrenic nerves. The intercostal muscles and supporting structures of the thoracic cage are supplied by the spinal thoracic nerves.

The pleura may be subdivided into several distinct layers in which are recognized: 1) a thin, delicate layer of mesothelial cells, 2) an avascular, subendothelial layer of connective tissue, 3) a loose areolar layer interspersed with elastic fibers containing numerous blood and lymph vessels, and 4) a deep layer reenforced by fibers from the adjacent pulmonary alveoli.

Considerations on Structural Alterations with Ageing

Following this brief description of the various anatomical and histological features of the tracheobronchial tree, certain observations on senescent changes which have not already been alluded to may be mentioned.

From a functional point of view the elastic tissue and smooth muscle of the lung are frequently referred to as the myeloelastic system. There is little reference in the literature to age changes in the smooth muscle. Wetzel (65) claims that despite an absence of mitosis and of amitosis, smooth muscle is capable of regenerating itself. Todd (66) reviewing Haggquist states that "smooth muscle, like cartilage and to a greater degree than that tissue, preserves its useful character even in advanced age". Perhaps an analogy may be drawn between the smooth muscle of the respiratory tract and that of the colon in which Ivy (67) discusses a "thinning" with age evidenced by the increased incidence of diverticulosis of the colon with advancing years. Together with the smooth muscle, the elastic tissue is vitally concerned with the complicated pattern of lung movement required by the respiratory act. During inspiration, the myeloelastic tissue elongates. The increased tension thus acquired provides the kinetic energy for active retraction during deflation. With elongation, there is a widening of the air tubes and a corresponding narrowing during expiration. Bending and torsion at the root of the lung are also dependent upon the nature of the elastic elements. While many writers (12, 15, 25) contend that the elastic qualities of the aged lung are impaired, histologically, there is little evidence of any morphologic change. Certainly, the loss of elasticity of the skin in old individuals is readily apparent, and a sluggishness of recoil of the lungs of aged persons at autopsy has been mentioned.

In the functional alterations of the elastic quality of the lung, factors at the biochemical or physiochemical level may be involved which the cytologist is incapable of perceiving. On the other hand, subtle variations in tonus accompanying the ageing process may be found in the governing or neural mechanism rather than in the myeloelastic tissue itself (Todd (66)).

Senescent changes in the striated muscles of the thoracic wall have already been described. At this time, it may be pertinent to add that the

diaphragm and abdominal muscles which are the two largest muscle groups concerned in the mechanics of respiration contain an abundance of elastic fibers. The degenerations in these muscles are similar to the intercostals.

Senescent atrophy of the epithelium has been described by Nascher (12) and Ashoff (13) as involving a wasting of the columnar ciliated epithelium, atrophy of the bronchial glands and loss of sensitivity of the mucous membrane. As a result, the mucus formed in the bronchi and bronchioles would be thick and tenacious. In disagreeing with this view, Warthin (30) claims that excessive secretions of the bronchial tree characterize old age. The occurrence of mitotic figures in tracheobronchial epithelium is rarely noted. Miller (39) quoting Bockendahl considers regeneration of the epithelium under normal conditions to be very inactive. The transition of the ciliated epithelium to the stratified squamous type is ascribed to low grade irritation or chronic infection and not solely to an age change. Macklin (59) feels that the nests of alveolar cells or epicytes may undergo malignant degeneration as a function of ageing.

The fibrous connective tissue making up the supporting framework of the lung constitutes the greatest bulk of this organ. Reference has already been made to Ward's (36) review of connective tissue changes with ageing in the discussion of the coverings of the thorax. Todd (66) dwells on the importance of the connective tissue in the nutrition of other tissues between which it lies, and quotes Maximow on its role in the defense mechanisms and hydration of the body. Senile deteriorations are apparently represented by a process of dehydration with a reduction in ground substance in which the sheet-like continuity is lost. Collagen fibers and tissue spaces appear more prominent histologically. Breathing dust and irritant laden air over long periods of time is stressed by Nascher (12) as causing pneumoconiosis which in turn stimulates connective tissue hyperplasia. However, he feels that this hyperplasia is a normal occurrence in involution with the irritant action of dust playing perhaps a small role in the excess proliferation of the connective tissue. Thewlis (15) also finds, at times, a proliferation of the fibrous elements with contraction resulting in impaired resiliency.

It is apparent that over the course of time, the connective tissue stroma acting as a depository for the countless numbers of minute particles inhaled from the surrounding environment, would acquire an increasing rigidity. The age changes depicted in the lymphoid elements would add its effect on the overall decline in flexibility and resiliency. Impairment of these functions of the supporting framework of the lung would seriously affect the complex movements of the tracheobronchial tree vitally concerned with respiration and bronchoelimination. In this connection, the findings of Saxton (68) are significant. His studies show that the lymphoid tissue in

the lungs of rats increases with advancing age to the extent that partial obstruction of the bronchial airway is produced favoring the development of chronic pneumonitis and bronchiectasis in over 80 per cent of his old animals. Environmental factors did not appear to influence the frequency of chronic pulmonary suppuration.

The relative infrequency of arteriosclerotic change in the pulmonary arteries as compared to the aorta and its branches has been commented upon by many investigators. The basic rationale proposed for this discrepancy involved a consideration of the differences in internal stress or pressure to which the two systems are exposed. Certainly, the newer concepts of inherent defects in lipid metabolism would apply as much to the pulmonary circuit as to the systemic arterial tree. The frequent association of pulmonary arteriosclerosis in advanced emphysema (69) would tend to add weight to the existing evidence that elevations in pressure within the pulmonary vascular bed predisposes to arteriosclerotic change. Karsner (70) makes the statement that pulmonary arteriosclerosis is frequent, being present in most cases of mitral stenosis and often found in such diseases as chronic bronchitis, emphysema and other chronic diseases of the lungs. In his opinion, however, "pulmonary hypertension is not an important cause of sclerosis". In reviewing the older literature, Nascher (12) mentions the occurrence of pulmonary sclerosis in the aged as a factor in the insufficient nutrition and subsequent waste of pulmonary tissue. Rolleston (25) quotes Roussy and Leroux who found frequent evidence of endarteritis obliterans and fibrosis in older individuals with "atrophous emphysema". This is substantiated by Thewlis (15) who feels that secondary changes may occur in the pulmonary arteries as a result of pulmonary hypertension resulting in obstructive endarteritis. Ashoff (13) finds a "senile thickening and widening of the pulmonary arterial walls" which does not correspond to the arteriosclerotic process as observed in the systemic arteries. When this is f[illegible]"

In describing the histology of [illegible] that the larger branches of the [illegible] tima due to age which seems to appear earlier than in the main trunk itself. He mentions Ljungdahl's series of senile pulmonary arteriosclerosis which was frequent after the age of fifty and "practically constant after seventy years of age". It affects principally the right and left pulmonary artery and their main branches presenting a small degree of intimal thickening with moderate fatty change. Anderson (72) also states that after seventy, intimal proliferation is frequently observed with moderate degrees of fat change. Normally, Wilens (73) found the pulmonary artery to be less elastic than the aorta in young individuals. While the elasticity

decreased with age, the rate of decrease was not as rapid as in the aorta so that relationships regarding elasticity were reversed in old age.

Of late, cytochemical studies have provided additional evidence regarding quantitative differences between the pulmonary artery and the aorta. Myers and Lang (74), working with the human thoracic aorta, found a gradual decline in elastin and creatine with ageing while the collagen appeared to rise. Lansing, Rosenthal and Alex (75, 76) in their studies on the human pulmonary artery found a slight but steady increase in elastin up to the 8th decade. The calcium content of the medial elastin of the pulmonary artery increased to a maximum of 0.66 per cent at the 8th decade as contrasted with an increase to 6.8 per cent in the aorta. They conclude that the low rate of calcification of medial elastic tissue of the pulmonary artery is an important factor in limiting formation of atheromatous lesions.

The changes in the smaller blood vessels are difficult to divorce from alterations in the pulmonary tissue and alveolar walls themselves. Pathologic processes as emphysema and pneumoconiosis may lead to an obliteration of the pulmonary capillaries so that the capillary bed is reduced. As a consequence of the increased fibrosis, the intima of the smaller vessels may show considerable fibrous thickening. In chronic bronchitis and bronchiolitis, the accompanying arteries become rigid and the increased formation of fibrous connective tissue may cause compression of the capillary network (71). Vischer (29) describes varying degrees of alteration and deterioration in the capillaries. They may be enlarged or shrunken; rigid and brittle or flabby. He asserts that the permeability of the capillary walls may be largely destroyed and the circulation of blood conspicuously retarded. It is probable that these are pathologic changes since studies on cell permeability seem to indicate a decrease with age (77). Roughton (78) found that the average time spent by blood in the human lung capillary under resting conditions was 0.75 seconds falling to 0.34 seconds when performing hard work. The total blood volume in the capillaries was 60 cc. at rest and 95 cc. at work indicating no extensive opening up of the capillary bed during exercise. There is presumably no data relative to age changes.

The reduction in sensitivity of the mucous membranes in older persons and alterations in the "governing" mechanism responsible for muscle tonus have been cited. Todd (66) points to the observations of Ellis in which the Purkinje cells of the cerebellum tended to disintegrate and disappear starting at about forty years. Kuntz (79) found histological changes consisting in moderate deposition of melanotic pigment and diminution in chromidial substance in the autonomic ganglion cells together with a progressive increase in the amount of connective tissue in the framework of the ganglia

associated with ageing. It is apparent that similar degenerations may be expected in the nerves and ganglia supplying the lung and would explain in large measure the decrease in irritability and conductivity present in senescence.

PHYSIOLOGIC CONSIDERATIONS AS INFLUENCED BY THE AGEING PROCESS

When structural alterations are exhibited by an organ or tissue, the physiologist can anticipate some degree of functional change. Frequently, he is disappointed at the apparent discrepancy or lack of correlation between obvious morphologic derangements and the ability of that organ or tissue to perform in a normal manner. Nature has been exceedingly kind in investing most, if not all, of the constituents of the body with a reserve capacity for exceeding the normal requirement. The respiratory tract serves as an excellent example of such benificence. The opposing view has often been commented upon: physiologic alterations in the absence of histologic evidence of structural change. Karsner (71) supports this contention in stating that the elasticity of the aorta may be impaired with no changes apparent in the aortic wall. Perhaps the ageing process saps the reserve capacities. This would follow from the statement of Boas (80) that when at rest, the bodily functions of aged persons are normal. The body temperature, blood constituents, respiratory exchange, cardiac output and renal function compare favorably with youthful individuals. But if exposed to unusual strain or stress, the range of response is curtailed and the ability to maintain homeostasis becomes impaired.

In presenting the physiology of the respiratory system, we are concerned with pulmonary function as such, and the mechanism of bronchoelimination serving to protect the bronchopulmonary structure. The intricate movements of the tracheobronchial tree, intrapleural and intrapulmonary *pressure relationships, lung volumes, intrapulmonary gas mixing* and diffusion, protective reflexes and the integrity of the ciliated epithelium are only a few of the essential factors which play an important role in respiratory physiology.

Bronchopulmonary movements

Although some dimensional changes in the thorax with respiration have been touched upon in the preceding section, Macklin (48a) presents an excellent picture of bronchial movement. During inspiration, the tracheobronchial tree not only becomes elongated but the lumina are dilated as well. With the shortening on expiration, there is an associated narrowing of the air passages. *Thus the bronchial framework with the attendant* blood vessels and other structures "opens up" bringing about an even and uniform expansion of all of the pulmonic substance. The direction of lung

movement on inspiration is downward, outward and forward into the expanding portions of the pleural cavity and away from the immobile posterior wall. The lung root and mediastinum must be flexible to permit these movements. The lower end of the trachea is not fixed but loosely held and the bifurcation is freely movable. The heart and great vessels readily adjust themselves to these root movements. These movements occur in all parts of the bronchial tree being relatively greater in the small than in the larger tubes. An even distribution of air throughout all of the pulmonary tissue is possible only through these adjustments of the bronchi and root structures.

An increase in the amount and density of the fibrous connective tissue and lymphoid elements as a consequence of ageing and pathological deteriorations has been described. Extension into the root zone and along the bronchial tree would impair the normal elongation and retraction of these structures. In addition, fixation of the lung root would permit little or no elongation of the apical bronchus and its branches which would seriously hamper ventilation of this region with imperfect aeration of a considerable segment of the adjoining zone. Macklin has coined the term "bronchosclerosis" for this rigidity and stiffening of the bronchopulmonary tree. While the effect of impaired bronchial movements on ventilation are apparent, the alterations in circulation and lymphatic drainage must also be considered. Drinker and Warren (81) in their study on pulmonary transudates note that the resultant of capillary pressure and oncotic pressure in the pulmonary bed makes for dryness. The movements of the lung are extremely important in aiding lymph flow. Crippling of the peristaltoid movements of the bronchi would interfere with adequate drainage exerting a deleterious effect on the self-cleansing properties of the lung and providing excellent soil for the propagation of pathology. In this connection, Richards (28) points out that the loss of linear elasticity of the bronchial tree is seen in certain cases of pulmonary fibrosis in which the trachea is jerked down on inspiration by descent of the diaphragm.

Pulmonary function

A considerable literature has accumulated on the mechanisms of pulmonary function. Baldwin, Cournand and Richards (82) in their comprehensive papers have suggested the following classification: 1) Ventilatory function involving the exchange of air between the lung and the environment and depending upon the integrity of the thorax and its supporting elements, normal structure and elasticity of the pleura and mediastinum, normally elastic and expansible lungs, patency of the airway, and a normal respiratory stimulus functioning as a coordinated neuro-muscular mechanism. 2) The function of respiratory gas exchange which is particularly

concerned with the effective distribution of inhaled air to the functioning alveoli, and with diffusion of the respiratory gases across the alveolo-capillary membrane.

In the main, alterations in ventilatory function producing varying degrees of insufficiency result from either obstruction of the pulmonary airway or a restriction in pulmonary expansion and contraction and is expressed clinically as dyspnea or difficulty in breathing. Impairment in respiratory gas exchange may be due either to the underventilation of relatively well perfused alveoli or the overventilation of portions of the lung receiving little or no blood. In addition, the diffusion of respiratory gases is dependent upon the network of pulmonary capillaries, a total blood flow through the lung adequate in volume and rate of flow and an alveolar capillary membrane permitting free diffusion of gases. The clinical manifestations of a disorder of gas exchange are anoxia and hyperventilation. An analysis of the state of pulmonary function is obtained from the measurement of volumes of air contained in the lung in different phases of respiration; the total pulmonary ventilation while at rest and at maximum stress, and the variations in the respiratory gases in blood and alveolar samples during different activity phases.

LUNG VOLUMES. *Vital capacity* defines as the maximum volume of air which can be expired after a maximal inspiration has been said by numerous observers to decrease with age. Bowen (83) tested 184 subjects between the ages of 15 and 85 years. There was no appreciable drop up to the age of fifty but then gradually fell to 50 per cent of the adult value at eighty-five years with the steepest decline occurring between 50 and 60 years. In conclusion, he states, "doubtless many factors produce a reduction in vital capacity after fifty but in the absence of definite disease all must be considered as manifestations of a normal ageing process". Myers and Cady (84) compiled data from the literature and their own series of 88 women and 118 men between the ages of 66 and 89 years. The figures for women averaged considerably lower than for men. The decrease in vital capacity was gradual for both groups after the age of 66 with the male series beginning with an average of 74 per cent of predicted normal and ending with an average of 53 per cent while the respective values for the women were 52 per cent and 44 per cent. Kaltreider, et al. (85) confirms the general concensus that the vital capacity is only slightly decreased from 40 to 50 years following which there is a more rapid decline. Those who continued to be active showed less fall than those retired from work. Arnett (86) calculated that the average loss per year in vital capacity averaged 33.7 cc. Miller (87) performed determinations on 744 men and found a decrease from 3,150 cc. (79 per cent of normal) at 40 to 44 years to 2,400 cc. (62 per cent of normal) at 90 to 94 years. The day to day variations in vital capacity of

the same subject has recently been stressed by Mills (88) who found standard deviations of between 45 and 293 cc. in 56 series of at least ten determinations. This is perhaps reflected in the wide range of values for normal subjects in the same age group obtained by Baldwin et al. (82).

	Age 16-34		Age 35-49		Age 50-69	
	Range F.	Range M	Range F.	Range M	Range F	Range M.
Vital cap. (supine in cc.)	2312–4150	2792–4950	2212–3435	3300–5240	1570–3525	2184–5420
Average	3057	4012	2830	4160	2431	3417
Ratio $\frac{R.A.}{T.C.}$	20 0		23 4		30 8	

(From Baldwin, E. de F , Cournand, A and Richards, D. W. Jr (82))

While the data indicates a progressive decrease in vital capacity with age, surprisingly high values were obtained in some of the older members of this series. The important factors determining the vital capacity which might be affected by the ageing process have been listed under ventilatory function.

Residual air represents that volume of air remaining in the lungs following a maximum expiration. Kaltreider et al. (85) found that the vital capacity constituted a smaller portion and the residual air a relatively larger fraction of the total lung capacity. When his values were grouped according to decades, there was a gradual decrease in the total capacity but the residual volume increased from 1.19 to 1.58 liters. He found that repeated measurements of the pulmonary capacity showed great constancy in the same individual and that the most useful capacities for classifying respiratory dysfunction are the vital capacity and relationship between the residual air and total capacity. While age had no influence on the mid capacity (end of quiet or resting respiration), the residual air constituted a larger per cent of the total capacity; from 19.8 per cent in the third decade of life to 31.5 per cent in the seventh decade. In the series studied by Baldwin, Cournand and Richards (82), the ratio of residual air, total capacity increased from 20 per cent in the young group to 30.8 per cent after the age of fifty. Hurtado and Boller (89) noted that this ratio varied with sex and age but rarely exceeded 35 per cent in normal individuals. It has been noted that the finding of a normal ratio is compatible with the existence of small localized areas of emphysema. Values over 35 per cent indicate that a relative state of hyperinflation or emphysema probably exists. Herxheimer (90) studied the relationship of the reserve air (the amount of air forcibly expressed from the resting midposition) to the vital

capacity in 123 patients. The normal ratio averaged 33 per cent whereas in patients with emphysema, the reserve air was 49 per cent of the vital capacity. This data must be accepted with some reservation since the ages of his two groups were not comparable; the patients with emphysema representing a much older age group.

Maximum breathing capacity expressed as the largest volume of air moved in and out of the chest as a function of time was found to have a significant negative correlation with age (82).

	Age 16–34		Age 35–49		Age 50–69	
	Male	Female	Male	Female	Male	Female
Standing MBC (Liters/min)......	126	93 7	109.4	89.3	90 6	73.5

(From Baldwin, E. de F., Cournand, A. and Richards, D. W. (82).)

It was felt that this measurement most effectively indicated any alterations in the "bellows like" function of the chest since it depended upon neuro-muscular coordination of chest movements, patency of the airway and normal elasticity of all pulmonary structures. Motley (91) supports this view in affirming that the maximum breathing capacity appears to have considerable practical value in the early detection of fibrosis with loss of lung elasticity and various degrees of bronchial obstruction.

Seabury (92) in summarizing the measurements of the pulmonary compartments states that it is difficult to find satisfactory normal figures for the various components of lung volume. "Predicted values must give due consideration to all variables, and the formulas for prediction must be derived from the analysis of a large number of normal representatives within each category of variability. This lack of normal volumina is especially striking for the age groups below sixteen..." and more so for those over 65 years! The effects of activity, a sedentary versus an outdoor occupation, must surely be considered one of these variables.

Distributory and Diffusion Factors. The *index of intrapulmonary mixing* employing an open circuit method has been reported by Cournand et al. (93) as furnishing evidence of the effective distribution of tidal air through the alveolar spaces during quiet breathing. In clinically normal subjects with a ventilation evenly distributed to the various parts of the lung, the nitrogen concentration of the 7 minute "wash out" sample rarely exceeded 2.5 per cent. Values higher than this were indicative of inadequate ventilation of pulmonary tissue. While this method has been employed in a large series of patients with pulmonary disease, no comparable figures are available for intrapulmonary gas mixing in different age groups. However, in Darling's (94) study on 18 normal subjects and 5 patients with

severe pulmonary emphysema, he noted that the three normal subjects over fifty years of age fell in a transition zone between the normal young adult and the clinically abnormal subjects. He raised the question as to *whether the lungs of elderly subjects could be considered entirely* "normal" with respect to effective aeration of the pulmonary alveoli. Both Fowler (95) and Comroe (96) have employed a single breath test using the Lilly nitrogen meter as a measure of the distribution factor. As with Darling's test, there has been no systemetized study of variations in the aged; although the factors involved (decreased elasticity of certain parts of the lung, regional obstruction to air flow, decreased expansibility of some areas of the lung and combinations of these) may occur to some extent in ageing.

Respiratory gas exchange consisting in the relationship between pulmonary ventilation and the respiratory gases at rest and after exercise has been the subject of intensive investigation within recent years. In reviewing the older literature, both Nascher (12) and Thewlis (15) state that the respiratory rate increases with age becoming more shallow and abdominal in character. This is in disagreement with Warthin (30) who claims the respiratory rate falls from 28 per minute in the newborn to 16 per minute in the aged with prolongation of the expiratory phase. In Baldwin's series (82), the mean figures for minute ventilation per square meter of body surface were remarkably constant. There was a greater tendency for the ventilation to be maintained at a higher level in the older age groups than in the younger during the first minute of recovery following exercise.

With ageing, Reichinstein (45) finds after a review of the literature, the amount of expired carbon dioxide diminishes. In the decade 55–65 years, the average carbon dioxide eliminated per minute is 204 cc. This drops to 166 cc. in the decade 65–75 with a further decrease to 129 cc. in the age group 85–93 years. Nascher (12) confirms this by stating that the amount of carbon dioxide expired in old age is approximately one-half that of maturity. Shock (97) reports an increase in the alveolar pCO_2 with increasing age with the carbon dioxide tension of the adult male higher than that of the female. This sex difference becomes significant at the age of thirteen and is thought to lie in certain physiological characteristics not present before this age Berg (98) also finds that with increasing age of his subjects (up to 68 years), there is an increased slowness of carbon dioxide elimination *during the recovery period from moderate exercise; the carbon* dioxide half-life recovery constants of a 60 year old subject is nearly double that of a 20 year old. The oxygen recovery constants are apparently less affected by age. Pace (99) studied the carbon monoxide desaturation in man breathing pure oxygen as influenced by age. The half-time of desaturation was found to increase by 1 per cent for each year above 40.

The studies of Robinson (100) and Baldwin et al. (82) indicate a slight decrease with age in the resting oxygen consumption per square meter of body surface. This averaged 146 cc. in the 16–34 year old group and fell to 132 cc. in the 50–69 year old group but was practically identical during the minute of standard exercise. The rate of oxygen removal in cc. per liter of ventilation was similarly reduced for the older age group both at rest and after standard exercise. Norris, Yiengst and Shock (101) found that with increasing work loads, each age group showed a greater increase in excess ventilation than the next younger group and the oldest group showed a greater increase in excess oxygen consumed than the two younger groups. *The arterial blood of normal young adults is between 94 to 98* per cent saturated with oxygen at rest and following moderate exercise. In the older age group above 60, the oxygen saturation is often reduced to 92 per cent. Motley (91) found that a comparison between the exercise arterial oxygen saturation and the resting value was highly significant. In the clinical evaluation of certain pathologic states as emphysema, the degree of impairment paralleled the decrease in arterial oxygen saturation with exercise. He felt that a true diffusion difficulty with increased resistance to passage across the pulmonary membrane was of minor significance in lowering the arterial oxygen saturation of the blood and that the primary disturbance was one of distribution.

In discussing the intra-alveolar mixing of gases and diffusion as a part of pulmonary function, the absence of data on any large group of subjects, particularly in the various age groups, is evident. The major factors governing the respiratory gas exchange; permeability of the alveolo-capillary membrane, diffusion gradients for the respiratory gases, and the activity of carbonic anhydrase have not been extensively investigated. Perhaps Comroe's (96) statement is explanatory; "Most of the newer tests of pulmonary function require expensive equipment and trained personnel and for some years to come their use will be limited to large medical centers. Wherever facilities exist, they may be used to establish normality or abnormality of lung function, to measure objectively the extent of alteration and to analyze the cause of this change".

Elasticity and Pressure-Volume Measurements. Air moves in and out of the lungs by virtue of the existence of a pressure gradient between the lungs and atmosphere. This pressure gradient is produced by the movements of the diaphragm and thoracic cage with the elasticity of the lungs and supporting structures playing an important role in the applied force. The viscosity of the inhaled air plus the resistance of the pulmonary airway and the inertia of the blood detract from the force exerted by this pressure gradient. The measurement of pulmonary elasticity and distensibility has been amplified of late through the introduction of new technics

and devices including the pneumotachometer (102). Kaltreider et al. (85) used the simple test proposed by Christie (103) to demonstrate alterations in pulmonary elasticity. Forty per cent of his series of older subjects showed a partial or complete disappearance of the reserve air after maximal inspiration. He attributed this to slight impairment in pulmonary elasticity and decreased mobility of the chest cage. After the fourth decade, he noted that Prinzmetal and Kountz found a reduction in ability to lower the intrapleural pressure on forced respiration. Paine (104) analyzed a group of 8 normal subjects ranging from 19 to 84 years (5 were over 58 years) employing the coefficient of distensibility which Christie and McIntosh (105) found to be the best clinical measure of pulmonary elasticity. He found no significant difference in the older age group. The elasticity studies employing volume: pressure curves by Lawton and Joslin (106) and Fenn (107) have not been applied to the investigation of changes with ageing. In fact, Fenn comments that "the data apply primarily to normal healthy young males and the variations to be expected in other age groups and in clinical practice are still unknown".

Bronchoelimination

The maintenance of the self-cleansing properties of the tracheobronchial tree is of vital importance to an organ constantly exposed to foreign agents such as irritating dusts, particulate matter and bacteria. The factors concerned in the protection of the respiratory tract are integrated by reflex activity so that gas exchange so necessary to survival is not impeded The hairs at the entrance to the nasal passages serving as a gross filter provide the first line of defense. These factors include ciliary activity, mucus formation, phagocytosis, cough and the peristaltic-like contraction of the bronchial musculature.

Coughing represents a complicated reflex mechanism generally initiated by irritation of the nerve endings in the bronchial and tracheal epithelium (108). The forceful expiration of air carries the offending material out of the bronchial passages. With the diminished muscle tone, decreased sensitivity to stimuli and slowing of reflex activity so common in the ageing process, the inability to produce an effective cough may result in an inadequate elimination of bronchial secretions in the older person and so predispose to pathologic states.

The flagging of the ciliary mechanism with age has been referred to. Hilding (109) studied the respiratory epithelium as a vital organ and found that the air flowing over the mucus blanket passes more and more slowly as it reaches the lung periphery while the area of the blanket increases markedly This facilitates humidification and the deposition of suspended matter. The pathways of the ciliary stream are fixed and recuperative and

regenerative powers are considerable. Negus (18) points out certain conditions present in ageing which affect normal ciliary activity: excessive drying and atrophy of the epithelium; chronic infection, and the integrity of the tissue fluids and electrolyte balance. In certain diseases of the respiratory system, Hilding (110) feels that death may occur from failure of the ciliary system. When this mechanism is lost, secretions may accumulate in such large quantity that death through asphyxia is possible.

The inhaled smaller particles which are not conveyed up by ciliary activity or by the rhythmic peristaltoid movements of the smaller bronchi are absorbed by the wandering phagocytes and make their way into the *circulation and lymphatics of the lung. Age deteriorations may be mani*fested in almost all of the intricate mechanisms concerned with bronchoelimination with the consequent impairment of the normal self-cleansing properties of the lung.

The Pathologic Physiology of Disease in the Aged

Although it is not the intention of this article to enter into a review of the diseases of the chest in the aged, a working knowledge of the pathologic physiology as modified by the ageing process become highly desirable. For more detailed descriptions of disease and particularly the therapeutic approach, the reader is referred to standard texts on geriatrics such as Nascher, Thewlis, Rolleston, Mueller-Deham and Steiglitz.

The problems of old age and disease while not identical are oftentimes so intermingled that it becomes impossible to distinguish between the depreciations which occur in the older individual due to ageing and those due to the insults of previous infections, trauma, intoxications, etc. (111). Pathologic processes may simulate and accelerate the conditions leading to senility, and the longer life lasts the greater the probability that changes due to disease will accumulate. In this connection, Saxton (68) has defined a disease of old age in a species as one which increases in frequency and/or severity to the end of the life span; and depending on the organ or system affected and upon the degree of interference with function of a vital organ, may become a determining factor of that life span. The fundamental principles cited by Thewlis (15) are worth restating at this time: 1) senescence is a physiologic entity like childhood and not a pathologic state of maturity. 2) that disease in senescence in a normally degenerating organ or tissue is not a disease as found in maturity but is complicated by degeneration. 3) that the object of treatment in senescence should be to restore the diseased organ to the state normal to senescence. Oliver (112) has posed this pertinent question: "how much of senescence is an inherent part of the individuals proper evolution and involution, is normal to him, and therefore, to be accepted; and what part of his final disintegration in

old age is the result of disease, abnormal, and therefore to be avoided?" It is possible that the answer to this question awaits a frontal assault with the accumulation of data, more extensive and varied, made possible by newer technics and appliances including the tools of biochemistry, cytochemistry and enzyme chemistry. Until such a time, if we are to "add life to years", any deterioration must be at first contained and then subdued.

Resistance to infection

The numerous degenerative changes in both structure and function of the respiratory system would be expected to alter the resistance to infection in the aged. However, in any consideration of natural resistance, the respiratory tract plays only a limited role. Aside from the factor of acquired resistance to many infections resulting from earlier disease, Perla and Marmorston (113) find that the aged individual is less reactive to stimuli with the finer central mechanisms of adjustment dulled and the speed of response diminished. The lymphoid tissue, macrophage system, and the spleen undergo atrophy with the capacity to produce antibodies diminished. The bone marrow, slowly replaced by fat and connective tissue loses its capacity to respond to infection. The processes of repair are impeded and may even cease to operate. There is atrophy of the glands of internal secretion many of which are intimately concerned with the underlying mechanism of natural resistance. Deficiencies of absorption and excretion, and nutritional deprivations lessen the organism's power to resist infection. In general, the influence of old age consists in modifying the character rather than initiating different forms of disease. Rolleston (25) states that diseases common to all or most stages of life are in old age less acute and dramatic, and more prone to be latent. Indeed, there is an amazing poverty of constitutional and local reaction to injury or infection.

Most of the knowledge concerning the problem of natural resistance in the aged is of a clinical nature. The application of animal experiment, such as the nutritional studies of Saxton and McCay, may help clarify some of these problems. Recently, Kalter (114) in studying the effect of age upon upon susceptibility to influenza virus finds that the virus multiplies more rapidly in young mice than in old ones. As age increases, more virus is required to cause death. There appeared to be no indication that an inhibitory substance was present in the older animals. On the other hand, Gunn and Sheehy (115) found no significant difference in the mortality rates when comparable doses of virulent tubercle bacilli were given intrabronchially to three groups of dogs of varying ages. Cavity formation, however, appeared twice as frequent in the older animals which was thought due to the greater rigidity of the bronchial walls of adult dogs. Calcification of the tuberculous lesions of the lung was much more frequent in the

younger puppies (66.6 per cent) than in mature dogs (3.8 per cent). Duca (116) noted that newborn guinea pigs and rats appeared to be more susceptible to experimental tuberculosis than older animals.

With the paucity of experimental data, a survey of clinical problems may yield more information on the diseases of the aged. It is of interest from a statistical aspect that a comparison of the leading causes of death due to respiratory tract disease reveals that in 1900 pulmonary tuberculosis was first with 195 deaths per 100,000 population with pneumonia second with 176 deaths. In 1946, pneumonia was sixth with 38 deaths per 100,000 and tuberculosis seventh with 36 deaths (111). The course of disease of the respiratory system has undergone considerable alteration as a result of the advances in management and therapeutics particularly in the field of chemotherapy and antibiotic agents.

CORYZA, "THE COMMON COLD". The common clinical experience that as age increases the rate for coryza in the family unit distinctly declines has been approached statistically by Collins and Gover (117). This is disputed by Monroe (118) who performed a survey on 7941 individuals over the age of 61 years admitted to the Peter Bent Brigham Hospital. He feels that "colds" are as "common and as upsetting" in old age as in other age groups. It is difficult to use Monroe's data for comparison since his sample constituted a hospital population. Although there appears to be no difference in the longevity of people living in different climates, there are certain factors; cold or inclement weather, confinement to the home with its poor ventilating systems, and the greater incidence of upper respiratory infection, which are conducive to ailments in the aged (119). The adverse influence of low humidity and nasopharyngeal infections on the ciliary mechanism has been noted.

BRONCHITIS. The acute form is reported by both Johnson (120) and Thewlis (15) as being fairly frequent in the old. It is associated with a tracheitis and often preceded by a severe "cold" or virus infection of the upper respiratory tract; but in the majority of instances, results from the acute exacerbation of a chronic bronchitis. Cough is frequently the most troublesome symptom.

Chronic bronchitis is perhaps the most common ailment of the aged. Sheldon (121) reports an incidence of 40 per cent in his sample of 477 individuals while Monroe (118) notes 272 cases in his series. While the term itself implies an inflammatory process, the opinions concerning etiology are varied. Nascher (12) preferred to use the expression "atrophic catarrh". Roper (122) analyzes the various factors grouping them under the headings: metabolic, nervous, local pathological conditions, environmental, and bacterial. He questions whether infection is ever primary and mentions Christopherson and Broadbent (123) who feel that chronic bron-

chitis is not basically a bacterial disease but due, primarily, to a prolonged irregularity of the respiratory vago-sympathetic system. As such, it is considered along with bronchiectasis, emphysema and asthma as a disturbance of the respiratory autonomic nervous system. The view that chronic bronchitis is in all probability a mild form of asthma in which classical paroxysms of dyspnea are lacking is taken by Lister (124). Representing as it does a motley group of causative features, it is not surprising that the pathology may be exceedingly varied. The mucous membrane may become atrophic or hypertrophic; changes in the bronchial wall include fibrosis with occasional destruction of the muscle elements and extensive fibrous replacement. With recurrent infection, all factors involved in bronchoelimination become impaired. Narrowing and obstruction to the airway may be the first step in the development of more serious types of disease such as bronchiectasis, fibrosis and obstructive emphysema. Therapy is discussed by Howell (125). In our experience, the prompt and effective response to the newer antibiotics when purulent secretions are evident may alter the course of chronic bronchitis in the future.

PNEUMONIA. Pneumonia, in all its forms, is a common cause of death after the age of fifty years. With the advent of antibiotic therapy in the past decade much of our statistical data requires extensive revision. Perhaps it is no longer possible to quote Sir William Osler that "pneumonia was for old people The Captain of the Men of Death". Brainerd and Kerr (126) report a 70 per cent drop in the mortality rate for pneumonia in the aged between the years 1941–1942 as compared with 1936–1937. While Dublin (127) claims that the chances of eventually dying from pneumonia and influenza are practically level thruout life, Thewlis (15) finds a sharp drop in mortality after the age of eighty years (fig. 1). Zeman and Wallach (128) state that the incidence of pneumonia has been reported as high as 2,000 per hundred thousand population in persons over 70 years of age compared with 640 in the 15–20 year age group. By the very nature of this group of diseases in the aged, they will always claim a respectable toll and the death rates in senescence will continue higher than at other ages of life. Indeed, the results of modern therapeutic methods in pneumonia are so much better in the younger than in older persons that pneumonia fatalities should eventually be concentrated in large measure amongst older people (127). This is reflected in the table by Heffron (129).

Age group	% Mortality
2–10	6
20–29	16
40–49	42
50–59	66
60–69	66
70–	82

The senescent degenerations present in the aged act to modify the typical pathology and symptomatology as seen in youth. Clinical features may be classical or so insidious as to be overlooked. Frequently, a chronic "cold" may progress to pneumonia with no dramatic change in symptoms. Occa-

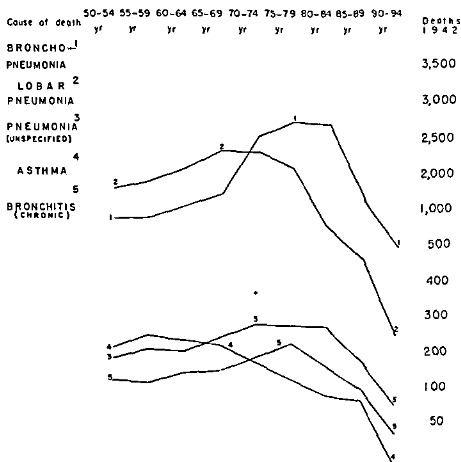


FIG. 1. Respiratory tract (from Thewlis, M. W.: The Care of the Aged. C. V. Mosby Co., St. Louis, 1946).

sionally, pneumonia may cause the sudden death of an apparently normal elderly person. Of prognostic significance, the coexistence of pathology elsewhere in the body is of major importance. Monroe (118) discusses the clinical picture in some detail. More than 95 per cent of his cases of lobar pneumonia were due to the pneumococcus, with type 3 being the most common. The bronchopneumonias were less well defined. The effect of senescent changes on the occurrence and course of pneumonia is noted by

Zeman and Wallach (128) who classified the following varieties: a) pneumonia due to specific organisms, b) due to filterable viruses, c) suppurative bronchopneumonia, d) of undetermined bacteriologic origin, e) aspiration pneumonia, and f) postoperative pneumonia.

Little is known about the immunologic responses in the aged beyond the statements made in the section on natural resistance. Kaufman (129) studied active immunization with pneumococcus polysaccharide and found no difference in mortality rate between the immunized group and a control group. The incidence rate however, was significantly lowered.

Bronchiectasis and Suppurative Diseases. Bronchiectasis and suppurative disease of the lung such as lung abscess are not peculiar to the aged and may occur at any age level. However, the senescent deteriorations particularly in the complex bronchoeliminative mechanism predisposes and accelerates the pathologic process. While the dilatation and destruction of the bronchial wall has its beginnings in recurrent episodes of bronchopneumonia in childhood, most writers agree that chronic bronchitis and related conditions inducing chronic cough are important contributory factors making for a viscious cycle (15, 80, 120). Repeated necrotizing infections of the bronchial wall result in a destruction of the mucosa with extension of the infectious process to the underlying muscle, elastic tissue, nerve fibers and blood vessels. Sante (57) points out that the severance of continuity of the diseased segment from adjacent areas of the bronchial tube renders it functionally useless so that the natural bronchial movements do not occur with respiration. Healing by fibrous tissue replacement leaves a permanently non-functioning unit which is subject to repeated infection. Inability to eliminate excessive secretions results in atalectasis of the lung tissue supplied by the involved segment. Monroe (118) feels that bronchiectasis in the aged is a much milder disease than that reported in the text books. Cough was not as striking a feature as in chronic bronchitis. "On the whole, bronchiectasis in old people seems to have been present for a long time as a fairly inactive process and is compatible with long life. But it can be aroused when a fresh pulmonary infection is introduced and then it may become serious."

Aspiration of foreign matter is more apt to occur in the elderly subject. The diminished sensitivity of the mucous membrane and the deteriorations in reflex activity impair the vital gag and cough reflexes. Suppuration is then enhanced by inadequate drainage. Saxton, Barnes and Sperling (131) found that an increase in the lymphoid tissue caused obstructive changes in the respiratory airway of old rats which appeared to play a major role in the pathogenesis of bronchiectasis in these animals.

Emphysema. In many of the earlier accounts, emphysema accompanying senescence was thought due to an atrophy of the alveolar walls as a

result of faulty nutrition. The waste of the alveolar septae permitted the air cells to coalesce resulting in the so-called "small chest" emphysema in which the thoracic cage was more or less rigid and respiration was carried on mainly by the diaphragm (Nascher (12), Thewlis (15) and Rolleston (25)). The work of Kountz and Alexander (31) served to differentiate two forms of emphysema.

Postural emphysema, frequently referred to as "senile" or "alveolar" emphysema is often encountered in older individuals. Amberson (132) states that practically all ageing people develop some degree of pulmonary emphysema. There are two views concerning pathogenesis; both of which depend upon the senescent changes of the ageing thorax and lung. Kountz and Alexander (31) feel that this condition is primarily the result of changes in the thoracic spine particularly of the intervertebral discs which has been noted in a previous section. The size of the thoracic cage is enlarged by virtue of these changes in the vertebrae and the lungs, in following the chest wall, become somewhat enlarged. As the lung is overdistended, thinning and atrophy of the alveolar septae take place with frequent rupture principally at the free margins and periphery. Macklin and Macklin (27), however, believe that "internal sclerotic" changes in all elements of the lung parenchyma due to the increased fibrosis limits the normal movements of the tracheobronchial tree including the lung root. This fibrosis may be a part of the ageing process or result from the numerous infections occurring through the years. The central portions of the lung are particularly hampered in their movements and only the periphery is capable of expanding along with the thoracic cage. The continuous stretching and over-distention of these peripheral alveoli finally causes breakdown of the alveolar walls. Darley and Kauvar (133) review the changes in the senile chest and the mechanisms of "senile emphysema". They point to a special form of postural emphysema occurring in the female as a consequence of post-menopausal osteoporosis of the spine.

In contrast to obstructive emphysema, measurements of pulmonary function are little, if any, impaired; nor is the arterial oxygen saturation of the blood significantly altered. Since the diaphragm is not affected, it retains its capacity for full excursion. In fact, breathing in the aged may be largely abdominal in type and unless there is marked loss of abdominal tone, interference with respiratory function rarely compares to that of obstructive emphysema. It may limit strenuous physical exertion or be an aggravating factor in other disease states.

Chronic hypertrophic or obstructive emphysema commonly occurs at a younger age level than postural emphysema but may escape detection for a long period because of difficulties in clinical diagnosis. In addition, pulmonary insufficiency from emphysema develops in the age group above

fifty because of a progressive loss in the elasticity of the lungs with advancing years. Two principal considerations are involved in the pathogenesis of this form of emphysema: impairment in elasticity or retractility of the lung, and obstruction to the free flow or air in and out of the alveoli. Frequently, both are implicated. Carr (134) feels that a primary, hereditary weakness of the elastic elements of the lung is the commonest cause while Macklin and Macklin (27) believe that intermittent or persistent spasm of the smooth muscle system leads to a narrowing of the air passages. This spasticity of the smooth muscle results from an inherited state of hypersensitivity or allergy. Because of a disparity in force between the two phases of respiration, air is trapped within the lungs and cannot be completely evacuated during expiration. Eventually, over-distention of the lungs impairs elastic recoil. As the lungs become more voluminous, the thorax tends to assume and become fixed in the inspiratory position The diaphragm is depressed and immobile; and the antero-posterior diameter of the chest is increased approaching the "barrel-chest" configuration.

Many, if not most, of these patients give a history of asthma or chronic cough which is probably allergic in nature. Comroe (96), however, emphasizes that in a number of his patients emphysema appeared to result from a single or repeated pulmonary infections such as pneumonia. One wonders if edema of the bronchial mucosa and the presence of excessive secretions could not have produced an obstruction to the airway similar to that resulting from bronchospasm. The known association of pulmonary fibrosis and anthraco-silicosis with emphysema has been the subject of many papers. Duguid (135) in a study of pneumoconiosis in coal miners states that emphysema is a condition which tends to develop and increase with age irrespective of occupation. Regarding the multiple causation of emphysema, Darley and Kauvar (133) affirm that "in all ages of life, the common triad that leads to emphysema is infection, allergy and occupational hazards".

With these structural and functional alterations, it is no wonder that all grades of pulmonary insufficiency and circulatory distrubance are encountered. Baldwin, Cournand and Richards (136) review the alterations in ventilatory function and respiratory gas exchange in 122 cases of chronic pulmonary emphysema. These were separated into four groups depending on the severity of pulmonary insufficiency as judged by the reduction in arterial oxygen saturation and the increase in carbon dioxide tension following a standard exercise test. The extent of hyperinflation or "trapping" due to latent bronchospasm not clinically apparent in many of these patients is spirographically illustrated by Bickerman and Beck (137) (fig. 2). Many patients with emphysema maintain an excessive pulmonary ventilation with the result that the arterial blood is almost normally saturated with oxygen. A marked fall in pulmonary ventilation occurs on the admin-

istration of 100 per cent oxygen (figs. 3 and 4). This finding, noted by Barach (138), was suggested as a simple guide to the efficacy of oxygen therapy in this condition. Furthermore, the impairment in respiratory gas exchange was accentuated by the reduction in ventilation consequent to oxygen administration. The carbon dioxide retention and disturbance in

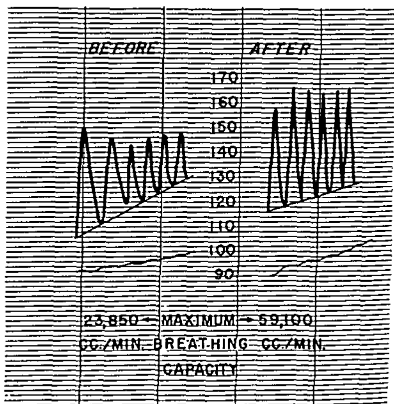


FIG. 2. Maximum breathing capacity before and after 0.5 cc. of 2.25% racemic epinephrin aerosol (from Bickerman, H. A., and Beck, G. J.: Ann. Int. Med., to be published).

acid-base balance is illustrated in figure 5. Clinically, Comroe et al. (139) find significant alterations in mental function accompanying these changes.

There appears to be sufficient evidence that chronic emphysema is a relatively common disease. Vischer (140) in reporting the post mortem findings on 1836 individuals from an old age hospital finds an incidence of 54 per cent. However, the marked discrepancy between the clinical and pathological findings in this disease has been emphasized by Monroe (118). There was agreement in only 4 per cent of his cases. In the clinical survey, advancing age increased the frequency of this affection.

Age group	% Cases of emphysema
61–65	8.0
66–70	9.4
71–75	12.1
76–80	14.7
81–85	22.5

(From Monroe, R. T. Diseases of Old Age Harvard Univ. Press, 1951.)

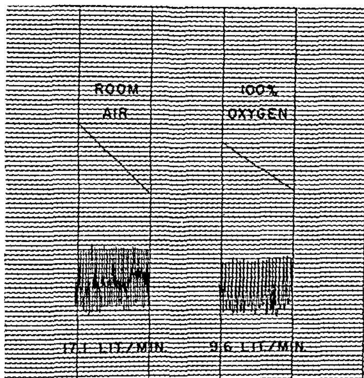


FIG 3. Pulmonary ventilation—breathing air + 100% oxygen in a patient with emphysema (from Bickerman, H. A., and Beck, G. J.: Ann. Int. Med., to be published)

Perhaps the application of newer physiologic tests to patients with suspected emphysema will provide a clearer concept of this disease and so increase our diagnostic accumen.

ASTHMA AND ALLERGY OF THE RESPIRATORY TRACT. The statement has been made that true asthma due to a sensitivity to specific allergins becomes less common with advancing years and Nascher (12) finds bronchial asthma rare in the aged. Both Johnson (120) and Boas (80) feel that it is possible but not probable for an individual to acquire allergic asthma after

the age of fifty. Multiple sensitivities principally to bacteria, is the major cause of asthma in the elderly. Taub (14) disagrees with this view and insists that frank allergy especially to the inhalants is quite common after forty years of age, and Rowe and Rowe (141) insist that food and inhalant allergies (rarely bacterial) are the usual causes of bronchial asthma in patients over 55 years of age just as with younger age groups. Forman (142) points out that skin tests are not as likely to prove helpful in older people as in young subjects. The dry, parchment-like skin may yield an

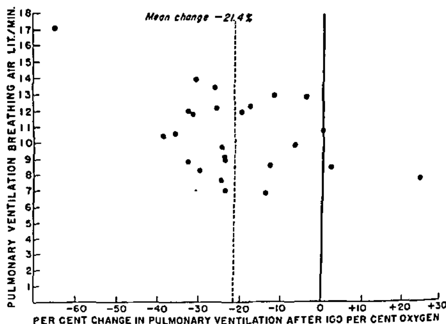


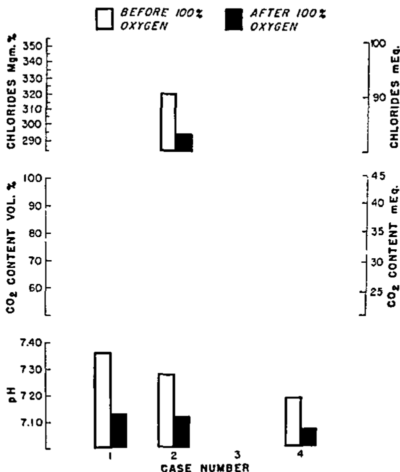
Fig. 4. Effect of breathing 100% oxygen on pulmonary ventilation in patients with pulmonary emphysema (from Bickerman, H. A., and Beck, G. J.: Ann. Int. Med., to be published)

atypical response to these allergins. In a statistical study, Fuchs (143) reports that 7.1 per cent of 507 allergic patients evidenced their first symptoms after the age of fifty years and that infection or bacterial allergy was the most common etiologic factor. This agrees with Monroe's data in which 80 per cent of the asthma was ascribed to intrinsic factors. The relationship of asthma to chronic emphysema has been stressed. The necessity for intensive treatment both from an allergic and anti-bacterial point of view hardly needs further discussion. An excellent review of the physiologic therapy of asthma is contained in a text by Barach (144).

Allergies affecting the nasal mucosa and upper respiratory passages have been referred to in a previous section. The deleterious effect of these con-

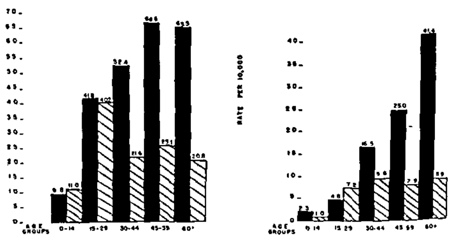
ditions on the ciliary activity and bronchoelimination may ultimately impair the defense mechanisms of the entire tracheobronchial tree.

Pulmonary Tuberculosis. The former belief that individuals who es-



caped tuberculous infection up to the age of forty were therefore immune and that there was little likelihood of acquiring such infection was based on the investigations at the turn of the century when pulmonary tuberculosis was almost universally acquired early in life. With improvement in the method of control of infection and a general betterment in the eco-

nomic and hygienic standards, this picture has been materially altered. There is a voluminous literature published within the past decade emphasizing the problem of pulmonary tuberculosis in older age groups. With the advent of microfilm screening, tuberculin testing and refined technic for the isolation of the tubercle bacillus, it has become apparent that old age is not immune to the white plague. Indeed, public health records show that pulmonary infection is common and the mortality unusually high in the aged. Boas (80) reports that the mortality increases from 62 per 100,000 in the age group 50–59 to 75 per 100,000 after 70 years of age. Myers (145) states that in persons over fifty years of age, the presence of



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communicable pulmonary tuberculosis is higher than at any other period. Case finding surveys from different regions of the United States report that the proportion of cases found increases directly with the age of those examined (146). From data presented by Amberson (132) and Beaven (147) there appears to be a real sex difference in infectivity after the age of thirty which does not seem to be due to differences in environment or occupation. In New York City, for the period 1941–1945, the mortality rate per 100,000 among white men between the ages of 50 to 69 years varied from 114–140, whereas the figure for women was 20 to 37. The incidence and death rates for tuberculosis in Rochester is graphically illustrated in figure 6.

Hebbert (148) claims that most cases of tuberculosis in the aged are due to the reactivation of old lesions and Boyd (149) offers support from

his follow-up studies in which he felt that most elderly patients acquired their tuberculosis sometime before the age of 40 years. However, it is becoming increasingly evident that the incidence of primary infection is increasing with age. In the elderly, tuberculosis is for the most part a chronic, slowly progressive disease tending to be indolent. The chronic fibroid type

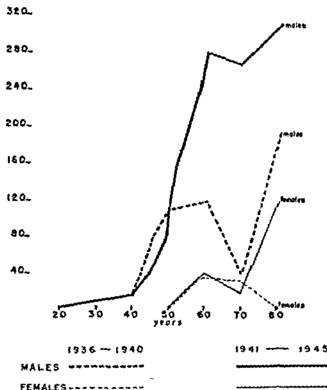


Fig. 7. Lung cancer incidence rates per 10,000 examined at various ages. Central Tuberculosis Station, Copenhagen. (From Clemmesen, J., and Busk, T.: Brit. J. Cancer 1: 253, 1947.)

produces few clinical symptoms and many patients with advanced disease are able to enjoy life and go about their occupations within limits. It is this very nature of tuberculosis in the aged which creates such a serious problem. "The elderly tuberculous are an important factor in the perpetuation of the disease throughout the world" (132).

Pulmonary Malignancy. Warthin (30) regarded the occurrence of cancer in old age as a coincidental manifestation of an intrinsic inherited fault which might appear at any age, and therefore, could not be considered a part of the major involution. Rolleston (25) notes that Ewing concurs

with this statement, yet an analysis of his data shows that there is a *continuous increase in the incidence of cancer at all age periods up to 85 years*, after which there is a slight fall. Statistics reveal that the incidence of bronchogenic carcinoma is increasing absolutely, as well as relatively. In a series studied by O'Keefe (150), 82 out of 131 patients with lung cancer were between the ages of 50 and 70 years (62.5 per cent). This is in contrast to Hayes' (151) figures in which the peak incidence occurred in the 40 to 60 year group. Males predominate in all series in the ratio of 4 or 5 to 1. An analysis of case material from the Central Tuberculosis Station of Copenhagen for the years 1936 through 1945 is plotted in figure 7 (152).

The etiology is as obscure as that of malignancy elsewhere in the body. At the present moment, it is an attractive concept to consider cancerous degeneration a genetic factor whose time-clock may be preset so that it appears at different ages and in different organs of individuals provided they live long enough. Senescence merely prepares the soil. The replacement of normal epithelium by less specialized cells (metaplasia) with the capacity for more riotous growth, the accumulations of irritant factors, changes in the nutrition and the electrolytic components of the cells and the involutionary processes in the endocrine system with disturbances in the delicate hormonal balance all contribute towards rendering the "soil" more fertile.

There have been several reports concerning pulmonary adenomatosis in man. Swan (153) finds this type of tumor in a considerably older age group than bronchogenic carcinoma. It is felt that these tumors may have multiple sites of origin arising from nests of alveolar cells or "epicytes" The sex ratio is not as marked as with bronchogenic carcinoma.

Summary

Basically, the problems of ageing insofar as they concern the respiratory system present features indistinguishable from other organs and tissues of the human body. In its pure sense, evolutionary change is governed by genetic inheritance which, if permitted to dissipate would end in final decay or dissolution. At present, it is impossible to separate the impact *of environment from this hereditary factor*, and much of what we measure is the summation of cause and effect.

Senescent deteriorations in the various portions of the respiratory tract have been described Completeness of description was dependant on the available data; and where this was lacking, brevity was perforce necessary.

Structural changes accompanying age, as visualized by the anatomist, were depicted for the tissues of the upper and lower respiratory tract. Alterations in the thoracic cage, head and neck were treated briefly. Much time was spent on the epithelial changes and age depreciations in the myelo-

elastic tissue because of their fundamental importance in the physiopathology of the lung. Functional changes involving the movements of the *tracheobronchial tree* with respiration, the physiologic approach to pulmonary function and the complex mechanism of bronchoelimination was discussed.

Finally, a short account was presented of certain diseases whose pathologic physiology was intermingled with the ageing process

Needless to say, there are many gaps in our knowledge concerning the aspects of ageing of the respiratory system. Perhaps if one system or one tissue or even one cell were fully understood many of our questions would be answered. To this end, an attack at all three levels employing the additional resources of cytochemistry, enzyme and biochemistry to reenforce the continued efforts of the histologist and physiologist may eventually throw light on the problems of ageing.

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23

AGE CHANGES IN RENAL FUNCTION

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The kidney is an organ which presents unique opportunities for studies upon the ageing process. It is also an organ where correlations between structure and function may be made (22). The development of new techniques for the functional evaluation of the kidney have made it possible to evaluate vascular changes and to make more or less precise estimates of other physiological processes such as filtration through the glomerular membrane and to study processes dependent upon the physical and enzymatic activities involved in tubular transport and the formation of specific compounds excreted in the urine.

The functional activities of the kidney include the following: (a) the formation of an ultra-filtrate of blood plasma, (b) the selective resorption of various substances from this ultra filtrate by enzymatic activity of cells comprising the epithelium of the tubule, (c) the selective excretion of substances from blood into the lumen of the tubule, and (d) the metabolic activity of the kidney in a formation of new compounds for excretion. From the blood delivered to the kidney, a filtrate containing all the constituents of the blood plasma with the exception of the red cells and the plasma proteins is formed. The rate of formation of this filtrate is dependent upon the amount of blood delivered to the filtering membrane and the pressure maintained by the action of the heart. As this filtrate passes down the tubule certain of the substances present in it are reabsorbed, as for example, water, sugar, chloride, sodium, etc. Other substances may be actively secreted from the tubules and added to this filtrate which is subsequently excreted as urine. In order to determine the amount of filtrate formed per unit of time, it is necessary to inject into the subject a substance which will pass freely through the glomerular membrane along with the other filtered substances that will not be metabolically changed or reab-

[illegible] amount of the substance [illegible] e. The substance which best meets these criteria has [illegible] ulin (25) Consequently the clearance of inulin serves as the most reliable estimate of the rate of formation of glomerular filtrate.

In order to estimate the amount of blood being delivered to the kidney, it is necessary to find a substance which will be completely removed from the blood in one passage through the kidney. Experiments on animals and humans have shown that these conditions are most nearly met by diodrast and para-aminohippuric acid. By determining the concentration of either of these substances in the blood and in the urine, as well as the amount of urine formed in a measured time interval, it is possible to estimate the amount of blood passing through the kidney per unit of time. Thus, if there is one mgm. in each 100 cc. of blood plasma, the appearance of 60 mgm. of the substance in the urine collected over a ten-minute interval means that 600 cc. of blood plasma have passed through the kidney per minute.

Additional information about the reserve capacities of the kidney with respect to transport mechanisms of certain substances can be obtained by raising the blood level of one of these substances to values so high that the kidney tubules are unable to handle more than a small proportion of that substance. Excretory Tm's may be determined for diodrast, PAH, phenol red, penicillin, etc., while reabsorptive Tm's for glucose, ascorbate, etc. may be measured.

In young adults approximately 600 cc. of plasma representing roughly 1200 cc. of blood passes through the kidney each minute. Of the 600 cc. of plasma approximately 20 per cent or 120 cc. passes through the glomerular membrane and appears as a filtrate. This 120 cc. of filtrate formed with an osmotic pressure equivalent to that of plasma passes down the tubule. During its passage approximately 119 cc. of the water are reabsorbed so [illegible] amount of urine formed is approximately 1 cc. per min. In ad[illegible] of water, all of the glucose present in [illegible] of sodium, chloride, and other [illegible] through the tubules the pH undergoes changes by [illegible] amounts of hydrogen ions, sodium, phosphate, and ammonia carried out through tubule activity. When the blood level of diodrast is raised to values high enough to saturate the tubular transport mechanisms, a maximum of 50–60 mgm. of iodine (Tm diodrast) can be excreted per minute, thus giving an estimate of the maximum functional capacity of the tubules. When plasma levels of glucose exceed the capacity for tubular reabsorption of sugar, the maximum transport capacity of glucose is determined

as approximately 350 mgm. per minute in the young adult. Although these tests of functional capacity may each give important information about a specific function, it should be pointed out that the result can be referred only to the total performance of this function by the kidney. It is not possible to draw inferences with respect to the activity of separate nephrons or functional units; that is, a reduction of 50 per cent in a Tm determination cannot tell us whether there is a reduction of 50 per cent in the number of functional units or whether the capacity of each tubule *is simply reduced by 50 per cent.*

Age Changes in Glomerular Filtration Rate

Figure 1 summarizes the data on inulin clearance obtained by the infusion technique (5) in 70 males between the ages of 20 and 90 years (4, 24). All the subjects were free from history or clinical evidence of renal disease, hypertensive cardiovascular disease, or cardiac failure. All the subjects were ambulatory and afebrile and tests were made under basal conditions. The average inulin clearance declined from 122.8 to 65.3 cc. per minute per 1.73 sq. m. between the ages of 20 and 90 years—a fall of 46 per cent. The regression equation, calculated by the method of least squares relating inulin clearance to age, gives the following equation:

$$Cl_I = 153.2 - 0.96a$$

where a is age in years.

Olbrich et al. (22) have compared inulin clearance in 10 subjects with normal diastolic pressure, age 65 to 80, with 16 subjects age 69 to 87 with high diastolic pressure. The average values for the group with normal diastolic pressures was 92.1 cc. per sq. m. per min. while those for the subjects with high diastolic pressures was 76.5. However, the latter group included females in whom lower values are normally found (25), and since the age distributions in the two samples was not identical, the differences cannot be ascribed to the effects of diastolic pressure changes alone. Similar results were obtained by using a single injection method rather than continuous infusions (21).

These results compared favorably with the observations on age changes in urea clearance reported by Lewis and Alving (14). At high urine flows, the urea clearance closely approximates the rate of glomerular filtration. Lewis and Alving made tests on 100 normal males between the ages of 40 and 90 and observed a gradual diminution in urea clearance. The regression equation for the prediction of urea clearance from age was:

$$Cl_{urea} = 136.6 - 0.912a$$

where a is age in years.

Clinical evidence for impaired glomerular filtration is often derived from values of blood urea content or plasma nonprotein nitrogen content. Lewis and Alving reported a gradual rise in blood urea nitrogen values rising from 12.03 mgm. per 100 cc. at 40 years to 17.62 mg. per cent at 89 years in their series. The regression equation for the estimation of blood urea nitro-

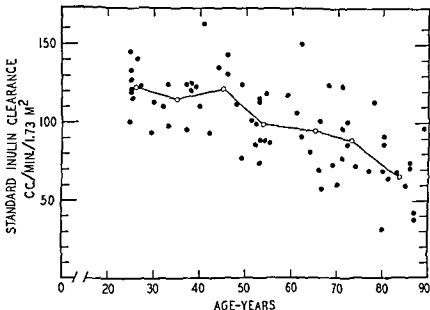


FIG. 1. Change in standard inulin clearance or glomerular filtration rate with age. O——O, average values cc. filtrate/mm./1.73 sq. m. body surface area. Data from Davies and Shock (4).

gen from age was:

$$BUN = 7.56 + 0.112a$$

where a is age in years.

Howell and Piggot (8) have reported blood urea levels in 103 cases (60 males and 43 females) ranging from 65 to 94 years of age. The average values increased from 34 mgm. per 100 cc. at age 65–69 to 37.9 in the group over 85 years of age. Observations of others, such as Amako et al. (1); Huffman (9); Laroche, Schulman, and Desbardes (12); Musser and Phillips (20); Rappleye (23); and Tully (26) indicate a tendency for blood urea values to increase progressively with age.

AGE CHANGES IN TUBULAR FUNCTION

Since one of the primary tubular activities is the resorption of water from the glomerular filtrate, the specific gravity of the urine offers a rough

estimate of the effectiveness of water resorption. Since the excretion of water is greatly influenced by differences in water intake, the specific gravity of casual urines has relatively little meaning. The most reliable values are those obtained on urines excreted under conditions of reduced water intake. However, most of the values of specific gravity of the urine available in the literature have been determined on first morning urine specimens (1, 15). For instance, Howell and Pigott (8) have reported measurements on Chelsea pensioners entering the infirmary of the Royal Hospital during the winter of 1940 to 1942. Specific gravity was determined on the early morning urine specimen on the day after admission. In 101 pensioners ranging from 65 to 93 years, the average value was 1.016. In general there was a decline in the specific gravity of the urine with increasing age, but the changes observed were irregular. On the other hand, when water intake was restricted for 12 hours preceding the collection of the urine specimen, Lewis and Alving (14) found that the specific gravity did not fall below 1.026 before the age of 65; above this age, values below 1.026 were obtained in 21 of their cases. The regression of urinary specific gravity on age was:

$$S.\,G. = 1.0364 - 0.00015a$$

where a is age in years.

More precise estimates of tubular function are afforded by determinations of the Tm. As stated before this determination is made by increasing blood levels of diodrast or PAH to values where the kidney is unable to remove all of the substance in one passage of blood. Figure 2 shows the values for standard diodrast clearance obtained in the 70 patients previously described (4). The average diodrast Tm fell from 54.6 to 30.8 mgm. of iodine per minute per 1.73 sq. m. between the ages of 20 and 90 years. This represented a reduction of 43.5 per cent. The regression equation relating diodrast Tm to age is as follows:

$$Tm_D = 66.7 - 0.40a$$

where a is age in years. A comparable reduction in PAH Tm with age has also been observed (18). In Olbrich's (21) studies, the average diodrast Tm for 10 aged males with normal diastolic blood pressures was 36 0 mg. per 1.73 sq. m. per min., while the value for 16 males and females age 69 to 87 with high diastolic blood pressures was 25.5 mgm. of iodine per 1.73 sq. m. per minute. Thus, there is clear cut evidence that with increasing age, the excretory capacity of the renal tubules is diminished.

The resorptive capacity of the renal tubules for glucose has been determined by Miller, McDonald, and Shock (19) in a series of 76 male sub-

jects free from clinical signs of cardiovascular, renal disease or diabetes. The average glucose Tm fell from 328 to 223 mg. of glucose per 1.73 sq. m. per minute between the ages of 30 and 90 years. The regression equation for the prediction of glucose Tm from age was:

$$\text{Tm glucose} = 432.8 - 2.604a$$

where a is age in years. When the regression is expressed as per cent decrease each year from a 100 per cent level set arbitrarily at 20 years of age,

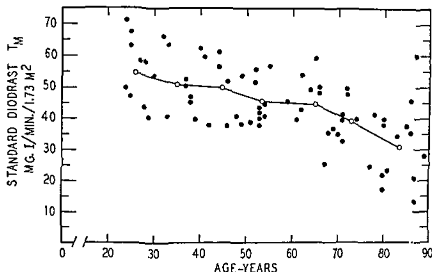


FIG. 2. Change in standard diodrast Tm with age. O——O, average values mg diodrast iodine/min /1.73 sq. m. body surface area. Data from Davies and Shock (4)

the Tmg decreases 0.68 per cent per year which does not differ significantly from that previously found for an excretory Tm (Tm diodrast).

Age Changes in Circulatory Factors

As stated previously estimates of the amount of blood passing through the kidney are based on determinations of the clearance of diodrast or PAH. Interpretation of clearances of diodrast and PAH as effective renal plasma flow is based on the observation that in young animals both of these substances are almost completely removed in one passage of the blood through the kidney; that is, at low plasma levels on the arterial side, venous blood from the kidney is practically free of them. Since it has been shown that *the maximum excretory capacity of the renal tubule is significantly diminished in old age*, it is necessary to demonstrate that sufficient capacity remains to permit almost complete removal of the substances at low plasma

levels before we can interpret clearance determinations in terms of effective plasma flow. Miller, McDonald, and Shock (18) have shown that the renal extraction ratio for PAH is not systematically influenced by age (table 1). The extraction ratio of approximately 90 per cent observed in the 27 subjects studied in this series compares favorably with the 20 subjects aged 18–49 years reported by Bradley (2); that is, 92.5 per cent in Bradley's study; 91.1 per cent in the present study. Furthermore, no relationship between the extraction ratio and the clearance of PAH was observed in these studies; consequently, it may be concluded that clearances of PAH and, by inference, diodrast are valid measures of plasma flow in the aged. It may also be inferred that the relative distributions of renal plasma flow to excretory and nonexcretory tissues are the same in old

TABLE 1

Renal extraction of PAH according to age decades compared with clearance of PAH

Age	Extraction of PAH			Clearance of PAH	
	Per cent			(cc./min./1.73 sq m.)	
	N	Range	Mean	N	Mean
years					
20–29	4	89.4–92.9	90.7	4	612
30–39	—	—	—	—	—
40–49	4	88.0–96.8	93.0	3	529
50–59	7	87.0–95.1	92.5	7	512
60–69	9	86.5–91.7	89.6	5	439
70–79	3	91.1–92.7	92.1	2	386

From Miller, McDonald, and Shock (18).

subjects as in young and that there is neither an absolute nor relative increase in the nonexcretory tissues perfused in the kidney of the older individual.

In the series of subjects studied by Davies and Shock (4), there was a decline in the effective renal plasma flow amounting to 53 per cent between the ages of 20 and 90 years (fig. 3). The regression equation relating the diodrast clearance to age is:

$$Cl_D = 840 - 6.44a$$

where a is age in years. Converted to percentage terms, the diodrast clearance diminished approximately 1 per cent per year. In the study reported by Olbrich et al. (22), the average values for effective renal plasma flow in 10 males age 65–80 with normal diastolic pressures was 489 cc. per sq. m. per minute, whereas the average values for 16 males and females age 69–87 with high diastolic pressures was 326 cc. per 1.73 sq. m. per minute.

The proportion of the plasma delivered to the kidney which is filtered through the glomerulus (Cl_I/Cl_D) shows a small but significant increase with increasing age (4) (fig. 4). Since the proportion of the plasma filtered is determined largely by the hydrostatic pressure maintained across the filtering membrane of the glomerulus (assuming filtration equilibrium to occur), *the increase in filtration fraction may be an indication that with increasing age there is a greater increment in vasoconstriction at the efferent side of the glomerulus than at the afferent*

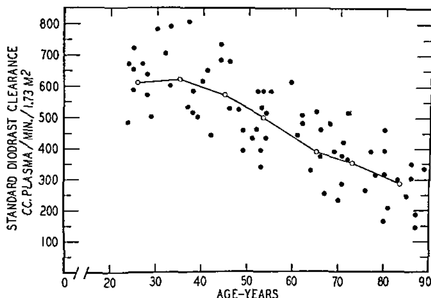


FIG. 3. Change in standard diodrast clearance or effective renal plasma flow with age. O——O, average values cc plasma/min /1.73 sq m. body surface area. Data from Davies and Shock (4).

The average inulin clearance per unit of Tm (Cl_I/Tm) remains constant between the ages of 20 and 90 (fig. 5). On the contrary, the diodrast clearance per unit of Tm (Cl_D/Tm) decreases from an average value of 12.6 at age 30–39 to 9.7 at age 80–89 (fig. 6). The constancy of the ratio between the glomerular filtration rate and tubular excretory capacity over seven decades is in accord with the hypothesis that a nephron loses its function as a unit. The steady decline in the effective renal plasma flow per unit of tubular excretory capacity beyond the fourth decade indicates that the average amount of blood delivered to each tubule (and by implication, each nephron) declines with age. This decrease in renal plasma flow with increasing age cannot be attributed to a reduction in cardiac output, since no estimates of cardiac output, crude as they may be, have indicated

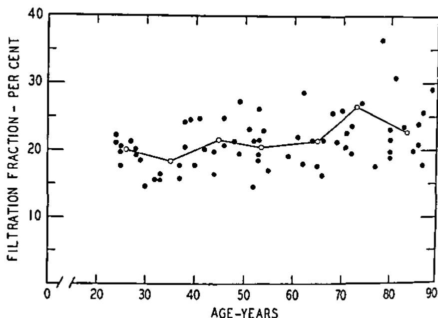


FIG. 4. Change in filtration fraction with age. O——O, average values. Per cent of plasma filtered Data from Davies and Shock (4).

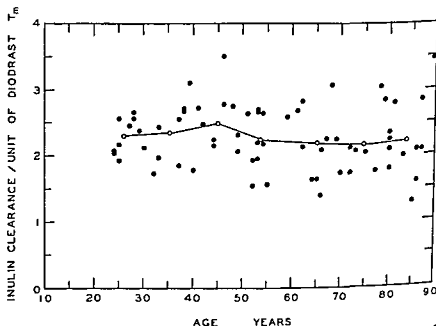


FIG. 5. Change in rate of glomerular filtration per unit of diodrast Tm. O——O, average values. Data from Davies and Shock (4).

a reduction of this order of magnitude in elderly subjects (13) Nor can it be attributed to decreased mean blood pressure since this tends to rise slightly with advancing age (17). Therefore, it probably reflects progressive vascular changes in the vessels supplying nephrons with blood.

Since vascular changes seem to play the important role in changes in renal function with age as reported above, McDonald, Solomon, and Shock (16) carried out a study to evaluate the functional status of the renal

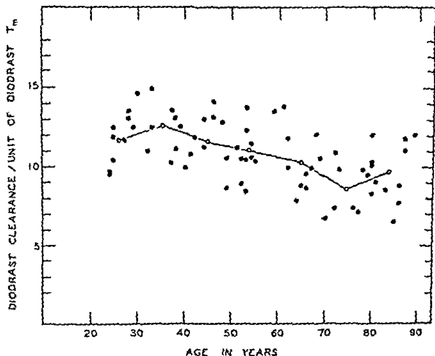


FIG 6. Change in effective renal plasma flow per unit of diodrast Tm O——O, average values Data from Davies and Shock (4).

arterioles in an ageing population. These studies were carried out to answer the important question of whether the vascular changes in the ageing kidney represented structural changes in the arterioles which were irreversible or whether the reduced renal flow could be augmented by vasodilating agents. Previous studies have shown that the administration of a pyrogen to young people resulted in a marked increase in effective renal plasma flow (3) It is believed that this increase in flow is in a large part mediated through a decrease in renal arteriolar tonus. Consequently, studies of the effect of the intravenous administration of a pyrogen on renal plasma flow were determined in 54 male subjects between the ages of 20 and 84 years.

The subjects were divided into three age groups: the young (Y), age 20–49, with a mean age of 36.6 years, N = 20; the middle (M), age range 50–69 years, mean age 58.8, N = 20; and the old group (O), age range 70–84, with a mean age 76.9 years, N = 14. Using the renal clearance technique of Goldring and Chasis (5), 11 20-minute urine collection periods were carried out starting out immediately after the intravenous administration of 50 million killed typhoid organisms (0.5 cc. TAB vaccine). Blood samples were obtained through an indwelling femoral artery needle. Sphygmomanometric blood pressures and pulse rate by one-minute radial artery counts were determined at the fifth and fifteenth minute of each period. *Mean values for each measurement were calculated for each of* the three age groups.

During the course of the pyrogen reaction in which a temperature rise was prevented by the oral administration of aminopyrine, no significant change in glomerular filtration rate was observed (fig. 7). On the other hand a significant increase in the clearance of PAH was observed in all age groups. Although the mean absolute increases were greater for the young than for the old group when the increments were expressed as per cent of the base-line values, the rise in C_{PAH} for the Y, M, and O groups was 76, 86, and 91 per cent, respectively. The filtration fraction (Cl_I/Cl_{PAH}) diminished markedly in all subjects indicating a fall in effective filtration pressure which would result from a greater vasodilation at the efferent than at the afferent side of the glomerulus, if there was no change in blood pressure. The absolute fall was greater in the O group than in the M and Y Groups. At the height of the reaction, the differences observed in base-line values between the age groups had completely disappeared.

The pulse rate increased significantly in all groups following the administration of the pyrogen and the systolic blood pressure dropped in the M and O groups, but remained constant throughout the reaction in the Y group. The small absolute changes in renal plasma flow in the older subjects following pyrogen are consistent with the anatomical findings of a progressive decrease in the renal parenchyma of the aged. On the other hand the time of onset and the percentage increase in renal plasma flow was similar in the different age groups; consequently, it must be concluded that the responsiveness to pyrogen in the vascular elements remaining in the aged kidney is not qualitatively different from that of the young kidney. The decrease in clearance of inulin and PAH with age may be explained on the basis of the decrease in the number of functioning nephrons, but the observed increase in filtration fraction cannot be accounted for simply on this basis. Since the administration of pyrogen is followed by uniform percentage increased in renal blood flow in all age groups; that is, filtration fraction fell to similar values and since the systemic blood pressure fell

rather than increased, it may be inferred that the renal arterioles are capable of dilating in the aged kidney. It may be concluded that the

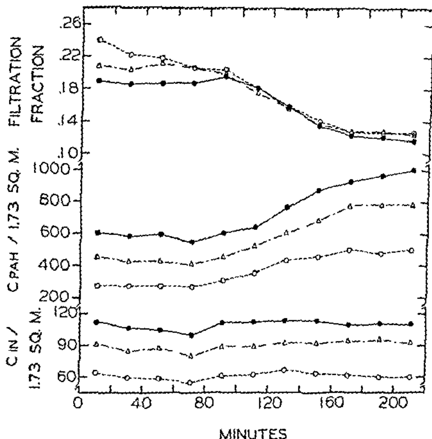


FIG. 7. Changes in glomerular filtration rate (C_{IN}), effective renal plasma flow (C_{PAH}), and filtration fraction during the pyrogen reaction. Fifty million killed typhoid organisms were injected intravenously at 0 time. ○——○, mean values for 14 subjects aged 70–85 years (0 groups). △——△ mean values for 20 subjects aged 50–69 years (M group). ●——●, mean values for 20 subjects aged 20–49 years (Y group). Reprinted from McDonald, Solomon, and Shock (16).

reduced renal blood flow observed in the aged is in part reversible and therefore not the result of structural changes in the renal vessels alone.

Age Changes in Renal Resistance[1]

The decreases in renal blood flow with age occurring without diminished blood pressure suggest a progressive increase in the resistance of the vessels

[1] The collaboration of Dr. Milton Landowne in the preparation of this section is gratefully acknowledged.

supplying the nephrons. The absence of a comparable reduction in cardiac output suggests that the kidney is predominately involved in any generalized increase in resistance. Since the renal blood flow may be temporarily increased by pyrogen in the absence of an increase in blood pressure in both young and old subjects, there must be a reversible or vasoconstrictive component operating to regulate the renal circulation of the old as well as the young individual. These general statements apply to the entire

TABLE 2

Estimates of resistance based on the renal response to pyrogen

Resistance†	Age				
	Young	Middle		Old	
	Vascular obliteration				
	0	*0*	*41%**	*0*	*62%**
Afferent					
Baseline	6.7	15.5	9.1	31.5	12.1
Residual after pyrogen	3.6	5.7	3.4	13.6	5.2
Change	3.1	9.8	5.7	17 9	6.9
Efferent					
Baseline	4.5	8.2	4.8	13.7	5.3
Residual after pyrogen	2.0	3.4	2.0	5 2	2.0
Change	2.5	4.8	2.8	8.5	3.3

* ... of the young ...).

† The resistance of each unit is considered to have a fixed component and a component removable by pyrogen. Data adapted from McDonald, Solomon, and Shock (16).

vascular supply to the kidney which includes the vessels leading to the kidney as well as to renal vessels themselves.

Various formulations have been developed to provide estimates of resistance for more limited vascular segments (6, 7, 10, 25). These define functional segments, but have been used, at least by implication, to relate to anatomically ... example as pointed out by ... arteriolar resistance are not expressions ... but apply to a larger vascular segment. The arteriolar resistance may constitute a different proportion of this segmental resistance in the older subject. In addition, many of the terms in the formulae utilize average values or approximations which may also change with age.

Useful information may be obtained from consideration of this calculated "afferent" segment resistance if its limitations are kept in mind. Thus "afferent" renal resistance, calculated by the formula of Lamport (10) increase markedly with age (table 2). These values are significantly

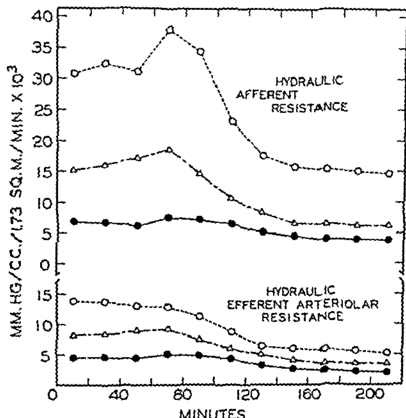


FIG. 8. Changes in calculated afferent and efferent renal hydraulic resistance during the pyrogen reaction Fifty million killed typhoid organisms were injected intravenously at 0 time O——O, mean values for 14 subjects aged 70–85 years (O group). △——△, mean values for 20 subjects aged 50–69 years (M group) ●——●, mean values for 20 subjects aged 20–49 years (Y group). Reprinted from McDonald, Solomon, and Shock (16).

lowered by pyrogen administration for all age groups (fig. 8). Although the reduction is greatest in the oldest group, the difference between young and old is not abolished by pyrogen administration. The increased afferent resistance remaining in the older group after pyrogen may reflect the morphological changes, largely sclerotic in the vessels of this segment. If the effect of pyrogen is primarily on the renal arterioles and smaller blood vessels, then the decrease in afferent resistance may be attributed to dilata-

tion in the preglomerular and glomerular vessels. Pyrogen induces greater vasodilation in the afferent vessels of the old than in the young kidney. Consequently, the afferent renal vessels of the old subject maintains a greater constriction in the resting state than over the young.

Further analysis of these data (11) has made it possible to evaluate the relative effects of loss of vascular pathways, increase in fixed resistance, and increase in variable resistance on the reduced plasma flow in the aged kidney. Since a loss of vascular pathways in a parallel arrangement will increase the net resistance without any change in calibre of the remaining units, estimates of changes in them must take into account the probable reduction in the number of parallel pathways.

It has been estimated (11) that in the kidney representative of the old group a vascular obliteration of up to approximately 60 per cent of the nephrons might have occurred. Under these limiting circumstances, efferent vascular segments would show no change in structural resistance or calibre (table 2). This is an extreme estimate and for lesser degrees of obliteration the remaining efferent segments would contribute to the increased resistance by structural narrowing. On the other hand the increased afferent resistance *persisting after pyrogen (table 2) cannot be entirely explained by a reduc*tion of even 60 per cent of the vascular branches. In addition a structural narrowing of the remaining afferent vessels must be postulated. This would make the residual or structural resistance of these vessels in the old as high or higher than that present in the young in the resting state where vasomotor tone is operative. In spite of this high residual afferent resistance in the aged, the vasoconstrictive resistance removable by pyrogen is greater than that in the young.

Thus although presently available data, as well as theory, leave much to be desired, they support the interpretation that there is, at the unit level, a vasoconstriction in the vessels supplying the aged kidney, since *the observed changes cannot be explained by alteration in vascular* arrangements.

It may seem somewhat surprising that vasoconstriction increases in the kidney with age, especially in the face of a progressive structural increment in resistance and obvious morphological obliteration. One possible meaning of this deduction would be that renal vasoconstriction is an untoward result of ageing, instituted by some local or remote processes which increase the tendency to metabolic unbalance. This would encourage a search for "Therapeutic" vasodilator. The danger of this analysis lies in the possible relative overemphasis it places upon the renal circulation. Although provided a great reserve and with a mechanism for receiving 20–25 per cent of the cardiac output, *the kidneys can function effective on 5–10 per cent* of the cardiac output.

An alternate hypothesis of greater appeal, despite its teleological nature, is that other organs of the body sharing the cardiac output with the kidney *are subject to regulation of their vascular supply*. The logistics of this problem require a resting excess, that is, a ready reserve. Under basal conditions this may efficiently be diverted to certain organs, among which is the kidney possessing both physical and functional capacity to handle as much as 25 per cent or more of the resting cardiac output. In many instances, activity of other organs is associated with a reduction in renal blood flow. The alterations which occur throughout the body with age, may require a redistribution of the blood which is being pumped. This logistic maneuver may be controlled as efficiently, or even less efficiently, in the older individual, but the increased renal vasoconstriction is a manifestation of this control. From this viewpoint one might well hesitate before trying to enforce vasodilation upon the older kidney unless the need was made evident.

Summary

With increasing age there is a gradual diminution in renal function as indicated by reduced rate of glomerular filtration, reduced effective plasma flow, and a reduction in both excretory and resorptive Tm's. *All the available evidence, up to the present time, indicates that the primary factor* involved in the reduction in renal function is based on vascular changes. However, not all of the changes observed can be accounted for simply on the basis of a reduction in the number of vascular pathways and a structural narrowing of the vessels which remain. The vascular bed remaining in the aged kidney is capable of responding to vasodilators as effectively as the vessels in young kidneys. In addition to the anatomical narrowing and loss of vessels, there is present in the aged kidney a persistent vasoconstriction which tends to reduce further the flow of blood through this organ.

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24

URINARY SYSTEM

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As a biological problem ageing of the kidney derives interest more from its theoretical implications than from the practical aspect of ill effects produced by the senescent processes. The relatively small place that disturbances of renal eliminatory function occupy in the picture of old age is however not due to any lack of senile change in the kidney but rather to the fact that, like most glandular organs, it contains so large a reserve of functioning tissue as to be rarely exhausted to the point of appreciable dysfunction.

General Evidence of Renal Senescence

That the kidney does grow old and lose its youthful adaptability to demands upon its powers of structural and functional growth is evident from the experiments of MacKay, MacKay and Addis (1). In this investigation there was not observed with old rats the same response of compensatory renal hypertrophy following the removal of one kidney as was found with young animals. During the first month of life, for example, there was 52.6 per cent increase in the weight of the remaining kidney over half the weight of the kidneys of a control group, whereas at one year the final replacement was only 32.3 per cent.

When an exact determination of the physical basis of this senescence is attempted a problem of difficult solution arises, for in the kidney, as in all tissues and systems of higher mammals, there occurs the complication of incident "pathological" disease that must be separated from the "normal" processes of ageing. The varied alterations in the human kidney that follow vascular change, the so-called benign and malignant nephroscleroses of the clinician, are examples of such difficulties. In these questions the final decision as to what are to be considered phenomena of normal senescence

will depend on the interpretation of the nature of the primary arteriosclerosis—an interpretation subject to wide variation, since it is often conditioned by the metaphysical aspects of the problem. For example:

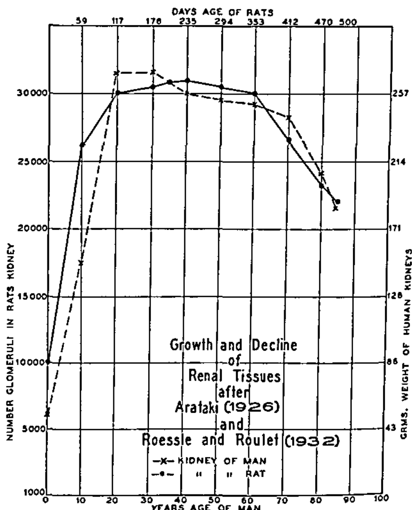


Fig. 1. The growth and decline of the renal tissues after Arataki (3) and Roessle and Roulet (2).

the implication of certain authorities that arteriosclerosis should be considered a "disease", since the acceptance of its involutional nature leaves no hope for prophylaxis and treatment.

The guiding thread that runs through all modern studies of senescence is the concept that its phenomena mark the orderly downward slope of a curve that ascended to maturity. It is indeed possible to construct graphs

representing the waxing and final waning of the renal tissue with the passage of years that have the general configuration of such a curve. Figure 1 shows the weight of the kidney of man (Roessle and Roulet (2)) and the number of glomeruli in the rat's kidney (Arataki (3)) from birth to senility. We are to be concerned therefore in this discussion, not with the fortuitous accidents of accumulated years, but only with changes "normal" to the life history of the individual and which fit with no disturbing effect into such an ideal curve.

If the problem of senescence is examined from this standpoint, the kidney proves to be a peculiarly fortunate example for study. For the "kidney" is not a specific and definitive organ but a group of organs, the nephrons, whose basic structures and function are similar but whose individual forms vary widely with environmental conditions Not only is this true in the phylogenetic series of the lower organisms but also ontogenetically in man. A large comparative material is therefore available for study. Only certain illustrative examples can be considered.

Phylogenetic and Ontogenetic Evidence

A most striking case of involution in the kidney resulting from ageing is the transformation that occurs in the mesonephros of the daddy sculpin (Graffin (4)). In the young fish the kidney is both structurally and functionally a "glomerular" organ but as it grows older alterations in both glomeruli and tubules change it to an aglomerular type. The glomeruli undergo various forms of degeneration—some becoming avascular and shrunken, others cystic or transformed into a necrotic mass of débris. Tubular disruption also is frequent, a constriction developing either at the origin of the tubule from the glomerulus or at some distance from this point. In this manner the glomerulus is separated from the tubule whose remaining portion persists as a functioning aglomerular nephron that is analogous to those units normally found throughout life in other fish.

Ageing in this instance has transformed the kidney so that the old individual possesses an organ that is structurally and functionally different from that with which it began life. In other fish, analogous though less complete degenerations are noted in the glomeruli with increased age (Graffin (4)). It is interesting to note in passing that the investigator of these lower forms was also confronted with the problem of separating pathological lesions from physiological involutions, for the kidneys of fish are commonly infected with parasites.

In mammals involutional change may be studied not in one kidney but in three, for the mammal has outlived two of his kidneys by the time of his birth. Our knowledge of the ageing and ultimate disappearance of the mesonephros is more complete than the life history of the poorly

developed pronephros. The work of Altschule (5) is of particular interest, for his description of the dedifferentiation of the nephron of the ageing mesonephros will be referred to later in discussing the senile involution of the nephron of the metanephros of the adult mammal. The number of capillaries in the glomerular tuft becomes smaller but simultaneously the cells of the secretory tubule begin to decrease in size so that the tubule becomes thinner, shorter and loses some of its convolutions. Disruption of the tubule is next observed, occurring either at the junction with the glomerulus or at some lower point in the nephron. The epithelium of these disrupted tubules may retain its normal appearance so that it is impossible in the histological section to distinguish between aglomerular tubules or vesicles and the intact nephrons. The ultimate result is the complete disorganization of the mesonephros and the incorporation of its remnants in other organs.

In the studies of Graffin and Altschule the cause of the degeneration and disappearance of structures is left unexplained. The involution of the organ is so completely accepted as an integral part of its life history that the mechanism of its destruction by implication at least is included in the processes of its growth and development. As a consequence of their living properties and characteristics the cells grow and differentiate and then in due course decrease and atrophy. To one whose interest has been turned toward the pathological aspects of vital phenomena, it would seem that, since these involutionary changes are distinctly degenerative, some disturbing mechanism must lie at the base of their inception and so be susceptible of examination. This idea receives support in the work of Gersh (6) who has correlated the structural and the functional involutional changes that occur in the mesonephros of embryo mammals. In this study it was found that the processes of elimination are continuous in the mesonephros and metanephros so that renal function is not interrupted by the involution of the mesonephros. The cause of the functional and structural degeneration of this organ is moreover directly examined, for in the words of Gersh, "the gradual loss of function (. . . and the structural change. . .) may be correlated with the disappearance or transference to other growing zones (sex organs, adrenals, diaphragm) of the arterial supply of the mesonephros. The shunting off of the arterial supply and the consequent reduction of the glomerular blood pressure is probably the primary cause of nephron dysfunction and degeneration."

By this concept the reciprocal degeneration and development of mesonephros and metanephros is made dependent on the relative change in the arterial supply of the waxing and waning organs, an observation first made by Hill (7). The theoretical importance of this hypothesis will become

apparent when the involution of the final kidney of man has been considered.

Renal Senescence in Man—Involution or Sclerosis?

So far it is evident that ageing of the kidney in lower forms and in the embryonic mammal is in the strict sense of the word an involution in which pathological disease plays no part. When ageing of the kidney of man is considered, the problem becomes more complex. Two questions must be answered: first, is there a primary abiotrophic involution characterized by a simple regression in size and differentiation of cells and nephrons? and second, are the alterations in the aged kidney that result from vascular change part of the normal life history of the organ or are they to be considered an aspect of vascular disease?

The second of these questions has been answered definitely by Jores (8) who has shown that the structure of the arteries varies with the passage of years from birth to senility. The sclerotic artery of the aged is as normal to that period of life as the thin and flexible vessel is to childhood, and the age of the individual can be roughly estimated by the histological appearance of his arterial walls. Any effect in the renal parenchyma secondary to such arterial alteration is therefore not pathological but as true a condition of senescence as the simpler and more direct involutionary degenerations that are so clearly manifested in lower forms and in the embryonic life of mammals.

Admitting the validity of the vascular (arteriosclerotic) component in the genesis of the senile kidney, the question remains if the simpler abiotrophic involutional changes also occur and if they can be recognized and distinguished from the effects of vascular disturbance. A priori, this would seem doubtful; for the involutional processes of atrophy, disruption and degeneration are just those that also result from vascular sclerosis.

In their study of the senile rats' kidney Moore and Hellman (9) have confirmed the earlier observation of investigators who found a decrease in the number of glomeruli. This reduction was apparently due to a process of gradual atrophy and complete disappearance of the structures which left no trace of their former state, so that the possible effects of vascular sclerosis are precluded. A similar mechanism may also exist in the atrophy observed in the old dog's kidney, for here arteriosclerosis is uncommon. However, since the dog is peculiarly susceptible to a true chronic interstitial nephritis the question is less clear than in the rat.

When past judgements concerning the problem in the human kidney are reviewed wide difference of opinion is found.

Fahr (10) dismisses the "senile kidney" of man in a paragraph as a

"benign nephrosclerosis" due to vascular change. Kaufman (11), on the other hand, devotes considerable space to the description of a senile kidney in which a peculiar primary atrophy of the tubules is followed by a disappearance of glomeruli. The description is general and no specific evidence is offered in support of such an hypothesis, though reference is made to the work of Furno (12). This investigator found in 70 old individuals 10 instances of what he terms "a typical senile kidney". The descriptions are also given in a general way that allows no detailed critical examination. It is stated that some organs weighed as little as 80 grams, while others were only slightly reduced in weight; that the tubules were diminished in size by an apparent reduction in their epithelial cells; that the stroma was arranged in orderly fashion. The arteries of some showed slight arteriosclerosis but in others arteriosclerosis was altogether absent. No indication is given of the correlation of these alterations. The remaining kidneys of the series showed various forms of vascular sclerosis. Furno's conclusion is that, though the arteriosclerotic kidney is the one most frequently observed in old people, it is not constant. The less common form of pure renal atrophy, which is never found except in old people, is therefore the typical senile kidney.

Between the extreme positions of Fahr and Furno stands Councilman (13). Though "three-fourths, certainly" of the kidneys examined by him showed arteriosclerosis, he nevertheless states that he hesitates to assign to this cause the alterations observed in the parenchyma. No changes not easily explicable by such a conclusion are described, however, nor are other more likely causes for the alterations offered.

These studies leave great uncertainty in the mind of the reader largely on account of the general manner in which the data are presented. For his personal satisfaction therefore the writer has examined histologically the kidneys from a general autopsy series of the last unselected 75 individuals over 70 years of age in whom no complicating renal disease was present. Every one of these kidneys showed an arteriosclerosis sufficient in his estimation to account for all the atrophic and degenerative changes that were present in the parenchyma. Apart from any possible variation in personal interpretation of the histological appearance, the vascular lesion was certainly of such degree as to make impossible the picking out among the varied pattern of arteriosclerotic scarring, atrophies and degenerations that might be due to some other cause.

Since, therefore (as Fahr has stated), it is impossible to separate benign nephrosclerosis of vascular origin from any simple senile atrophy of the kidney, *a consideration of the arteriosclerotic kidney* will describe in realistic terms at least the typical kidney that is found in aged man.

Structural Changes of Senile Nephrosclerosis

Regressive processes

The large and middle sized arteries are frequently affected though the changes may extend into the arterioles. Any sharp separation between the two forms of distribution as distinct morphological entities seems unwarranted, because gradual transitions are noted between the two extremes; and the functional disturbances, at first inconsequential, also rise gradually to the level of clinical appreciation with the increasing involvement of the arterioles.

The alterations in the renal arteries are part of processes occurring generally throughout the arterial system with the advance of years. As Jores has shown, there is a continuous modification of the structure of the vessel wall which may be regarded as a normal adaptive process. One of the most striking anatomical expressions of this evolution is the duplication of elastic fibrils and the development of a "hyperplastic" intimal thickening (fig. 2). The change in the terminal arterioles is of simpler nature, consisting of a thickening and hyalinization of the vessel wall. Accompanying the sclerosis in both large and small vessels there may occur a deposition of lipoidal material. Oppenheimer (14) has studied these changes in detail and found that they begin in infancy and can be observed in ever increasing degree with advancing years.

The parenchymal modifications that follow the vascular change are the result of disturbances in the nutrition of the tissues and may be considered examples of ischemic atrophy. The distribution of these effects throughout the organ are determined by the distribution of the vascular change, so that a kidney not greatly reduced in size with a relatively smooth surface and scattered retracted scars is found when the larger and middle arteries are irregularly affected, while a general reduction of the size of the organ and a more diffuse granular scarring follows the involvement of smaller vessels and arterioles. The details of this distribution of the various changes in the different branches of the renal artery and their relation to the parenchymal modifications are fully described by Zacharjewskaja (15).

The parenchymal change may be followed in both histological section (fig. 3) and by microdissection of macerated tissue (Loomis (16)). The glomerulus is affected either by collapse of its capillaries when the afferent arteriole is obliterated or hyalinization may extend into the tuft from the arteriole (fig. 4). By either process the tuft is transformed into a fibrous nodule and in the end may disappear (fig. 3). Quantitative examinations of the senile kidney of man have shown that in the seventh decade the number of glomeruli equals only two-thirds to one-half the early adult

count (Moore (17)). Atrophy of the tubules also occurs, recent past theory *assuming that this is due to glomerular destruction. A criticism of this* hypothesis has been given in another place (Oliver (18)) where it was shown that when examined in the continuity of dissected material there is little correlation between the size of glomerulus and tubule (fig. 5, *1*) and

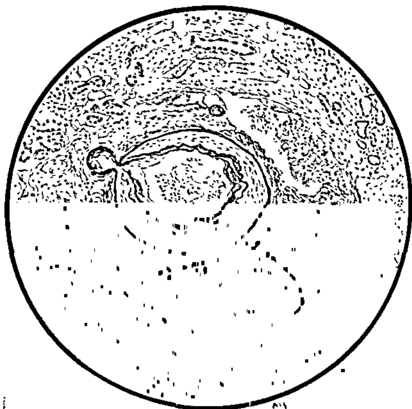


Fig. 2. Hyperplastic intimal thickening of renal arteries in benign nephrosclerosis (after Addis and Oliver, 1931) Magnification 50 ×.

that the tubule of the nephron does not constantly degenerate after glomerular destruction. The writer therefore sees no reason to suppose that atrophy of the tubule is not the result of the same factor that causes atrophy of the glomerulus, namely the ischemia due to vascular obliteration. The epithelial cells of the tubule decrease in size (fig. 4), it narrows to a shortened tenuous thread and the coils of the proximal convolution lose their complexity (fig. 5, *1*, *2*). So great may the reduction in its diameter be that thirty nephrons have been found in microdissected material to occupy the space formerly filled by three (Loomis (16)). The ultimate fate



of the shrunken nephrons is similar to that of the functioning elements of the kidney (mesonephros) of lower forms and the embryo. Tubular disruption occurs and the scars are filled with detached vesicles and cysts which lie among dense connective tissue (fig. 5, *3*).

Besides retrogressive alterations in the shape and contours of the



FIG. 4. The extension of fibrosis from the thickened afferent arteriole (shown in two sections) into the glomerular tuft. Tubular collapse and atrophy are also present (after Addis and Oliver (19)). Magnification 200 X.

nephrons, degenerations are noted in the constituent cells of the tubules. These take the form of the milder expressions of cellular regression such as cloudy swelling and fatty metamorphosis. The proximal convolution is particularly prone to such damage so that either its entire extent or irregularly isolated coils of its loops appear a glistening refractile white in the isolated specimen (fig. 5, *4*).

The atrophy and disruption of the parenchyma, occurring in scattered areas among better nourished and preserved tissue, is the essential mechanism in the formation of the arteriosclerotic scar. As a consequent result

of the reduction in the bulk of the nephrons the fibrils of the interstitial connective tissue framework are approximated and condensed. There is little evidence of an inflammatory component, such as round cell infiltration, in early arteriosclerotic scars. As they increase in extent and age such a reaction does occur along with an irregular proliferation of fibrils, though throughout their course the chief histological distinction between the changes that characterize the simple senile arteriosclerotic kidney and pathological malignant nephrosclerosis of vascular disease is the relative absence in the former of inflammation and its destructive effects on the parenchyma of the organ.

Adaptive changes

So far the changes described in both vessels and parenchyma have been retrogressive and their presumable effect is to decrease the function of the organ. It is less well recognized that in both elements of the kidney and not in parenchyma alone progressive changes occur; and since the direction of their functional effect is converse to the destructive lesion, and the degree of their development is proportional to the sum of the retrogressive changes, it seems reasonable to suppose them adaptive in nature and compensatory to the destruction of functioning tissue.

In the parenchymal nephrons hypertrophy of the tubules that lie outside the sclerosed vascular beds is observed (fig. 3). Its extent and distribution can only be properly appreciated by microdissection of the complete nephron from glomerulus to collecting tubule (fig. 5, *4*). Under these conditions of examination it is interesting to note that the change is limited almost entirely to the proximal convoluted tubule, other portions of the nephron remaining essentially unaltered. Hyperplastic lengthening of this segment may also increase its volume (fig. 5, *5*, *6*) so that in the end one proximal convolution may equal in amount of functioning tissue that of 12 or more normal units. There is no constant relation noted between the size of the glomerulus and its proximal convolution in either tubular hypertrophy or hyperplasia; the corpuscle may be normal in size, enlarged, atrophied or destroyed (fig. 5, *4*, *5*).

Progressive change in the arteries takes the form of a growth and new development of vascular channels (fig. 6). It is the generally accepted theory that in the normal kidney all the blood passes through the glomerular capillary bed before reaching the intertubular network for no significant number of direct branches from the renal artery to the tubular capillaries exist. It should be noted in passing that there has not been at all times agreement among anatomists in regard to this concept of indirect tubular blood supply and that some have claimed that direct branches do occur.

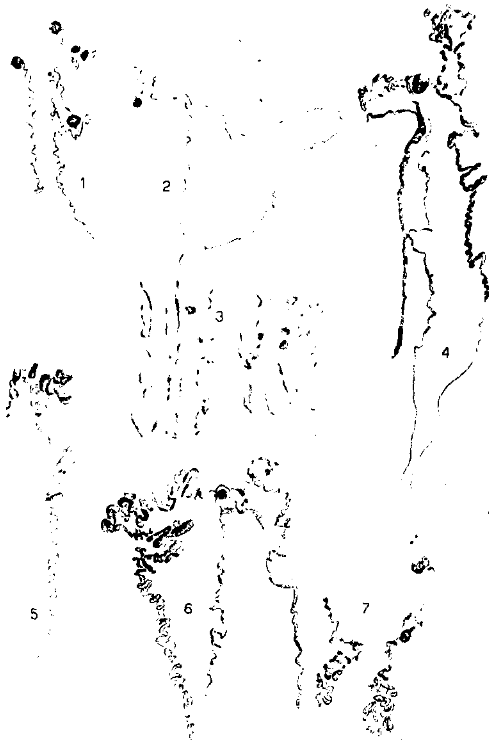


Fig. 5

The problematical existence of arteriae rectae verae is a well known example of such uncertainty and to this question we shall return after a description of the vascular apparatus of the arteriosclerotic kidney has been given.

In a kidney that shows a well developed sclerosis of its arteries there are found a great number of direct arterial branches to the intertubular network (Loomis (16)). The new paths consist of the following sorts. 1) Ludwig's vessel, a small branch of the afferent arteriole that leads to the intertubular network (fig. 6, *1*, *2*); 2) lateral branches from the interlobular artery (fig. 6, *3*, *4*); 3) arterial branches from the arcuate arteries and deeper interlobular vessels that, passing to the medulla, form arteriae rectae verae (fig. 6, *5*, *6*); 4) anastomoses between the afferent and efferent arterioles (fig. 6, *7*). Associated with these changes in the arterial tree is *a growth of new capillaries that surround tubules and glomeruli in an* adventitious network and so vascular connections are formed between structures not originally united.

To return to the problem as to whether the "normal" vascular bed of the kidney includes direct branches, the solution of a long continued controversy is found in the realization that the normal life history of the arteries includes the development of sclerotic changes. As previously mentioned Oppenheimer (14) has shown that they begin early in life and that they are found constantly in later years. The conclusion is obvious, therefore, that the adaptive and probably compensatory development of new vessels must also be considered a part of the life history of the renal arteries and characteristic of the structure of the senile kidney. Vasa rectae verae, therefore, are not "normally" found in significant numbers in the kidney of the young adult, though in the kidney of 70 years they are "normal" constituents of the arterial tree. It is of interest that all the new formed arteries eventually may undergo the same sclerotic changes that were in the first instance the *cause of their development*.

FIG. 5. The parenchymal changes in nephrosclerosis (Oliver (20)). Magnification 15 ×



Fig. 6

Functional Disturbances of Senile Nephrosclerosis

Structurally the kidney of the aged is an organ whose original parenchyma and vascular supply is reduced, but which presents a varying and usually proportional, degree of compensatory change in both of its constituent elements. In theory a functional balance might be expected. A complication, however, is found in the fact that though the parenchymal changes of atrophy and of hypertrophy may be considered a quantitative restitution in their functional effect, with the development of new vessels there has occurred a qualitative change in the sense that a different sort of blood supply has developed. The blood that formerly passed through the glomerular capillaries, and which there underwent certain modifications, is now being directed in ever increasing amount directly to the tubules. What change in renal function results from these altered conditions we cannot even surmise.

The complexity of the change structure of the kidney would be enough to make hazardous any attempt at a detailed interpretation of the functional disturbances noted in renal function of the aged, but they are only a part of the complications that make our understanding of the situation difficult. For the change in the renal arteries in Gull and Sutton's (21) classic phrase is only part of a general "arteriocapillary fibrosis" of the vessels of the body and this disturbance of vascular balance reacts upon

Fig. 6. The vascular changes in nephrosclerosis (Oliver (20)). Magnification 15 ×.
1. Fragment of interlobular artery from outer cortex showing Ludwig's vessel and its termination in the intertubular network.
2. Ludwig's vessel ending in a capillary brush.

3. Capillaries arising from vessels with no sign of formerly existing glomerulu[illegible]. Other abnormalities are beading with fat and the apparent obstruction of the lumen of the main vessel.

the function of the kidney. It is with a very considerable hesitation, therefore, that an attempt is made to discuss the function of the senile kidney in the brief confines of the present chapter.

Due to its great reserve of tissue, the eliminatory capacity may be normal or any part of normal depending on the balance of parenchymal scarring and compensatory change that have occurred within the organ. In the majority of aged people depreciation of kidney function is not a major difficulty, for other systems, such as heart or brain, similarly involved by vascular change, fail more rapidly and more disastrously. It is perhaps true that those urinary disturbances that do occur are more the result of circulatory abnormality than of the change that senescence has produced in the kidney. Albuminuria and cylinduria may be so slight as to be within the normal limits of earlier years. The concentrating power of the kidney is not greatly affected. No disturbance may be noted in the elimination of water, though the aged often complain of the inconveniences of a nycturia. In part this may be more apparent than real, a result of lighter sleep or of irritations of the bladder. When actual, it is, according to Volhard (22), a polyuria compensatory to a lessened day output that in turn is the result of incipient cardiac failure and circulatory embarrassment. The ability to eliminate nitrogen may be decreased, as evidenced by a lower urea clearance, but an abnormal rise of blood urea does not commonly result (Lewis and Alving (23)). In a more recent study Davies and Shock (24) have found that inulin clearance, diodrast clearance and diodrast Tm decreased linearly beyond the age of 30 years, the average fall from 20 years to 90 years being respectively 46, 53 and 43.5 per cent. The filtration fraction showed a significant rise between the third and ninth decades. The authors conclude their summary by the statement that "lack of experimental evidence precludes the definition of these mechanisms for the observed charges." It may be pointed out, however, that Dock (25) found that resistance to perfusion reduced the flow through the vessels of the kidney 32 per cent in the age group 45–60 years under what was observed in the 18–32 year group. As this investigator puts it "by fifty-five the average man in good health has been robbed by age of over one-fifth the original vascular bed".

If this is the picture of the function of the average and therefore "normal" senile kidney, it seems paradoxical to the writer, a pathologist, that a little more of the same change in kidney and heart and the gradually resulting disturbances of renal function that ensue should be placed in the category of the "abnormal" or pathological and therefore not be considered a part of senescence. Every gradation may be seen from what has been described above as "normal" to those cases where in the very

aged altered structure and disturbed function may lead to nitrogen retention and other evidences of renal impairment These cases, as Volhard has shown, cannot be considered examples of the so-called malignant hypertension and nephrosclerosis. And if, as many pathologists believe, the changes in the kidney of malignant nephrosclerosis are not so much qualitatively different as due to differences of tempo and distribution of the vascular lesion, then where is the line to be drawn between "normal" senescence and the "pathological"?

Such questions are perplexing enough when only the eliminating function of the kidney, concerning whose mechanisms we are relatively well informed, are considered. But there are other activities of this organ whose importance recent investigation is confirming.

General Effects of Renal-Vascular Senescence

It has been stated that the disturbance in renal function may be more the result of circulatory dysfunction than of renal structural change. The common cardiovascular disturbance of old age is the result of or is associated with or expressed by a hypertension, and the speculations that originated in Bright's first suggestion that renal abnormalities were concerned in its origin seemed in 1937 to have received their final objective and experimental conformation in the demonstration of Goldblatt (26) that restriction of blood flow through the renal arteries results in a continued elevation of general blood pressure. Is then the hypertension so frequent to some degree in old age as to be in a sense physiological (Saller (27)) the result of arterial change in the kidney?

Moritz and Oldt (28) studying arteriolar sclerosis in a series of hypertensive and non-hypertensive individuals have found that though the arterioles of the body generally are affected in increasing degree with age, the changes in the arteries of the kidney alone are constantly associated with hypertension. Of 100 non-hypertensives, one-third of which were over 61 years of age, none showed a severe alteration in the arterioles of the kidney and in 16 the changes were only mild. *In 100 hypertensive individuals on the other hand 97 per cent showed renal arteriolar involvement,* in 47 per cent the change *being severe. In the words of these investigators it would seem that "the effect of the renal arteriolar sclerosis in human hypertension appears to* be the functional analogue of the renal arterial clamp *in experimental* hypertension."

The implication of these investigations would therefore be to place senescence of the kidney in a distinctive position among the ageing process, for apparently by reactions originating in this organ might be determined the nature of the old age that an individual is to have and even the manner

in which that last period is to close. If a theoretical description may be permitted, and no other is possible at the present, the train of sequences would be described as follows.

As a part of the senescent process there develops a generalized sclerosis of the smaller arteries. Other factors fortuitous or "pathological" may influence the course of the vascular alteration, but with this we are not at present concerned. The vascular change within the various tissues and organs may be severe, but there is no evidence that suggests the conclusion that these lesions produce an elevation of blood pressure. If the arterial change within the kidney is severe however, hypertension follows. Depending on the degree of renal arterial involvement the hypertension may be "benign" and senility ends with mild circulatory difficulties and a benificient broncho-pneumonia; more grave, and cardiac failure or cerebral accident, depending on the condition of the local vessels, terminates in more dramatic fashion life's last episode.

By such a concept it is not so much vascular senescence, common to all organs and tissues, that determines the ultimate outcome, but a disturbance within the kidney and peculiar to its functions that may be the final and actuating mechanism of senile circulatory failure and accident.

Most certainly there are other mechanisms which may be the cause of hypertension in the aged and these factors will doubtless be discussed in their appropriate place. Here we are concerned with the kidney; it still seems true to say that only if its arteries be spared does senescence approach the biological ideal of a gradual and peaceful decline.

Summary

In lower vertebrate forms and in the embryonic mammal degenerative changes are observed with ageing of the kidney. Senescence in these instances has been looked upon as a primary parenchymal involution due to a decrease in the "vital energy" of the cells.

If such a primary senescent involution occurs in the kidney of man, it is obscured and its effects over-shadowed by secondary tissue changes that develop as a result of the normal ageing of the renal arteries. Ageing of the human kidney becomes therefore a special case of ageing of the vascular system.

A possible solution of this antithesis may ultimately be found in a further extension of those investigations which have shown that the supposed "primary" structural involutional changes in the ageing kidney of the embryo mammal are correlated with the retrogression of blood vessels and the transference of the blood supply to other growth zones. Vascular alteration would thus become the determining factor of the senescent change in the kidney of both man and the lower forms.

The disturbance of renal function in aged man is determined less by the degree of change in the functioning parenchyma of the kidney than by circulatory failure, an accompaniment of similar senescent changes in the cardio-vascular system. In only the unusual instance is the factor of renal failure important, and such an eventuality is not a part of "normal" old age.

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25

THE FEMALE REPRODUCTIVE SYSTEM

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Periods of growth—phases of activity—processes of involution: these form the well delineated pattern of the female reproductive system. This is, in essence, the problem of ageing.

There are many facets of gerontological interest in connection with the female reproductive system. Four mile posts, however, invite particular attention. Consideration of these foci of interest, together with a brief discussion of the history and the action of the ovarian hormones, will constitute the skeleton of this chapter. 1) The female reproductive system follows a constantly recurring pattern of growth-activity-involution, as the individual progresses from conception to sexual maturity. 2) The climacteric with its major landmark, the menopause, represents the termination of both the growth period and the activity phase of ovarian economy. 3) The ultimate involution of pelvic viscera, senility, is associated with the dominance of previously repressed complicating disease, and yet it occurs while other body systems, organs or functions are working at a close approach to maximum efficiency. 4) Significant involutional processes of the pelvic viscera may be completely reversed (other than ovarian function) under controlled hormonal influence.

The History and Action of Ovarian Hormones

It seems almost impossible to believe that the open door policy to the seemingly inexhaustible storehouse of ovarian steroid information was initiated only thirty years ago. By the early efforts of such men as Edgar Allen and George Corner the first steps of recognition were taken in the long sequence of events that ultimately led to the isolation and the synthesis of the ovarian hormones.

The follicular hormone (theelin) was first obtained from the ovaries of pigs by Allen and Doisy (1) in 1923 and was recognized by its ability to reproduce sexual (estrous) cycles in castrated mice and rats. This hormone reaches a high concentration in the fluid which forms in the ovarian follicle as the egg ripens and was therefore called folliculin. It is really a growth hormone, especially active upon the genital organs, for it causes increase in size in the vagina, uterus and mammary glands. It was found that injections of this hormone not only stimulate growth but also produce sex drive or mating reactions (estrus) in most castrated animals. This led to the final adoption of estrin or estrogen as a name for this ovarian growth hormone.

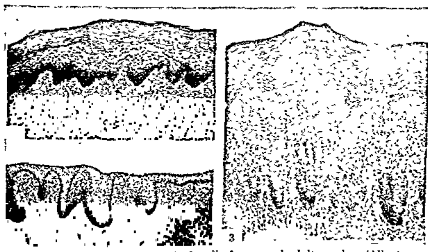
When previously unstimulated pelvic viscera are exposed to estrogen in satisfactory amounts and for a sufficient length of time, there occur waves of growth in the genital organs followed by an expected marked increase in blood supply and tissue fluid. This generalized tissue activity is followed by increased cell multiplication. Secretory activity then occurs in some of the genital tissues (endometrial or cervical glands, for example). Allen, Smith and Gardner (2) described this latter phenomenon in 1937. The effect of estrogen stimulation is by no means limited to the organs of reproduction, however, but spreads throughout the entire body. Richter and Hartman (3) first produced periods of spontaneous activity—rats running in rotary cages—by injections of this ovarian hormone. Widespread physical and psychic changes in the aged female have also been observed subsequent to ovarian hormone stimulation and will be discussed in detail in Section 5.

It is also interesting to note that the function of different organs requires varying amounts of hormone stimulation. For instance, maximal growth in the vagina of a castrate rat may be produced by a certain amount of estrogen (one vaginal unit), but it will require considerably more hormone to induce full growth and even early secretory activity in the uterus and endometrial glands (10 to 20 vaginal units). In addition, not only maximal amounts of hormone must be present but they must be present for long periods of time to produce full growth of the mammary glands. To be specific, it requires about eight months of estrogenic stimulation to grow the rudimentary mammary glands of a young male monkey to a size equivalent to those of an adult nonpregnant female, as demonstrated in the experiments of Gardner and van Wagenen (4). Thus, different animals, and different tissues within these animals, present quantitative stair-like thresholds of hormone sensitivity for different reproductive activities, either in phases of growth or sexual interest.

That actual cell multiplication takes place under estrogen influence is demonstrated by the examples in figures 1, 2, and 3, which are sections of

vaginal epithelium in the monkey. They show first the normal tissue (fig. 1). For comparison the tissue is then shown after castration (fig. 2), and finally subsequent to stimulation with estrogen (fig. 3). The senile atrophic vagina which is demonstrable subsequent to menopause is similar to the castrate section in appearance.

Soon after injections of this growth and activity stimulating hormone are stopped, degenerative changes begin in the genital organs. Within three weeks after removal of estrogenic stimulation from the monkey, the vaginal epithelium resembles figure 2 in atrophic changes. It remained



of

for Corner (5, 6) to provide some of the earliest information available concerning the involutional characteristics of tissue which has been removed from access to estrogenic stimulation. This work was done in monkeys, which are relatively ideal laboratory animals for the study of the actions of hormones in primates. The monkey has a sexual cycle which is similar to that of a woman—menstruation of three to five days duration occurring on an average of every twenty-eight days. In addition, however, there is in monkeys a reddening and swelling of the sexual skin which also depends upon ovarian hormones and is a good outward sign of the relative concentration of these hormones within the animal.

Removal of the ovaries from the monkey is followed by degenerative changes in the vagina, uterus and mammary glands, as in women, and by the disappearance of the reddening and swelling of the sexual skin. If the

ovaries are removed about the mid-point between the two menstrual periods (primarily the follicular portion of the cycle), a menstrual period follows the operation in four to seven days, and then menstrual function disappears. This phenomenon of bleeding roughly a week subsequent to oophorectomy has been termed in recent years "estrogen withdrawal bleeding". Menstruation or estrogen withdrawal bleeding was first produced experimentally in monkeys by Allen (7) after removal of the ovaries by injection of ovarian follicular hormone extracted from pig ovaries. Treatment of from ten to fourteen days stimulated the growth of the uterus and other genital tissues and returned the color and swelling in the sexual skin of previously castrated monkeys. Again after injections were stopped, an interval of four to five days ensued, and vaginal bleeding began. It is also possible to produce estrogen withdrawal bleeding in very immature monkeys as well as in the mature castrated variety.

After the experimental production of menstruation in ovariectomized monkeys, the actual process of menstrual bleeding was visualized by observation of menstruation in ocular transplants. The principle points in Markee's (8) description of this accomplishment are extremely interesting. The operation consists of transplanting small pieces of the lining of the monkey's uterus into the anterior chamber of her eye where the blood vessels of the eye grow into the transplants and afford a new blood supply. A day or even less before menstruation appears the circulation of the blood is impeded by a general constriction of the superficial vessels. After this vasoconstriction has persisted from four to twenty hours, a few vessels begin to open. Their endothelial linings have apparently been damaged and blood escapes to form small lakes just beneath the surface. A few vessels spurt and then close. This type of individual action probably explains why there is a great variation in the amount of blood loss with different individuals at the time of menstruation. It also explains why students of the menstruating uterus such as Bartelmez (9) have described great variations as to the amount of hemorrhage in different parts of the same uterus.

Our concern so far has been limited to the effects of estrogen. If ovulation occurs, the walls of the follicle from which the egg has been extruded undergo transformation into the corpus luteum, and the cells involved change their type of secretion to produce the second ovarian hormone, progesterone. This hormone quickly begins to develop changes in the lining of the uterus that makes implantation of the embryo possible. Although Bouin and Ancel (10) described these physiological changes in the endometrium known as progestational proliferation as early as 1910, it remained for Corner and Allen (11, 12) to provide the information necessary to establish a firm knowledge of the function of the corpus luteum and of the

physiological activities of progesterone. The process of changing the growth period of the uterine endometrium into one of physiological activity (secretory function of endometrial glands) rests with the influence of progesterone, when its presence is superimposed upon that of the growth hormone, estrogen.

Progesterone has the additional physiological function of preparing the endometrium for the successful implantation of fertilized ova. As a part of their work, Allen and Corner (13) castrated rabbits after they had ovulated and carried the animals to term and normal birth through injections of progesterone. A supplementary endocrine mechanism is therefore superimposed upon that which is adequate for nonpregnant sexual cycles. It probably involves not only the corpus luteum but also the placenta in some animals for the completion of normal pregnancy.

Besides describing the process of menstruation, Markee's observations have allowed him to settle a very important point, namely, that the menstruation which occurs after ovulation is similar in all essentials to the menstruation which occurs in the absence of ovulation. From the experimental evidence available, menstruation is probably a bleeding which *occurs during the degenerative phase of the cycle. This means that either* the ovarian hormone, estrogen, or a combination of the ovarian hormones, estrogen and progesterone, which had previously been stimulating growth and activity phases in the uterus, are either removed from a position of dominance or are no longer exhibited in concentrations sufficient to sustain growth or activity of the endometrial tissue. Subsequent to this change in hormonal concentration, the degenerative process occurs which terminates in the flow of blood that is termed menstruation.

Probably the clinching point in the argument of nonspecificity of menstrual flow was presented by Corner (5) as early as 1923 when he demonstrated specifically that ovulation need not occur at all and still an apparently normal menstrual flow will occur. It would seem that as follicles develop at the end of a previous menstrual period, more estrogen is produced to cause a growth phase in the uterus. The added tissue grown requires more hormone support. If the threshold of estrogen concentration is not raised sufficiently to continue growth, or if there is a decreased production of the hormone, degenerative changes begin within the endome*trium itself. The primates' menstrual bleeding is one of the terminal phases* of this degenerative process.

Following this line of thought, even the menopause can be interpreted as a result of the reduction of ovarian follicular hormone to that point where growth is no longer induced in the pelvic viscera and permanent involution occurs.

Many observations of the human ovary show that the function of

of puberty to 5,000. Similar conditions have been described for the human ovary, and students have often wondered just what the factor is that determines why one egg shall live and grow to maturity while another dies.

This elimination of ova is also an instance of the multiple processes of involution, or retrogression, which occur throughout the life of the individual; they are not confined to fetal life or the immediate postnatal period. This involution is compensated for by the formation or growth of new eggs. The marked decrease in the number of eggs in the ovary of the ageing individual might then be explained by a decrease in replacement rather than an increase in death rate. This recalls Minot's (16) emphasis upon the fact that involution may go on more rapidly in the young individual, or even in the embryo, than in the older person, but compensation occurs by the ability of the young individual to replace cells, whereas cell replacement or growth potentiality declines in old age. As far as the uterus, vagina or mammary glands are concerned, the factor which produces cell division or growth of these tissues is available in the ovarian hormones. The reasons for the lack of ability to replace or the causes for decreased production of cell division are still unknown.

Adolescence

The term adolescence (adolescere—to grow) has an unusually effective application to our discussion of the process of ageing in the female reproductive system. If we are to have the phase of mature activity, followed by the menopausal and senile processes of involution, we must first have the period of growth.

We should deviate at this stage from strict adherence to a discussion of the female reproductive system to discuss the adolescent pituitary in some minor detail. Actually very little is known of gonadotrophic activity during the growth years in either the female or the male. Freed (17) in reviewing this subject stated that prior to adolescence little or no gonadotrophic substance was excreted in the urine and that during and after adolescence appreciable quantities were measurable. It is relatively certain, however, that the waves of follicular activity so characteristic of the adolescent ovary are basically stimulated by the previous production of follicle stimulating hormone in the pituitary. The best laboratory evidence to support this contention was supplied simultaneously by Smith and Engle (18) and by Zondek and Aschheim (19) in 1927. Not only does the follicle stimulating hormone affect the gonads, but estrogen and testosterone in turn react upon the pituitary. Injection of estrogen causes changes in the pituitary that can be seen microscopically. The suggestion has been made that the growth of follicles in the ovary during adolescence might be the initiating factor influencing the pituitary to begin its influence upon

the ovary. At present, however, the evidence seems to point to increased pituitary function initiating a change in the ovaries. Suffice it to say, the flush of estrogen produced by the growth of follicles in the ovary during adolescence provides a growth factor not only for the pelvic viscera but for the general body physiology as well.

A definite indication of increased ovarian hormone activity, as evidenced by an increase in the excretion of estrogen in the urine of girls during adolescence was reported in the figures of Dorfmann, Greulich and Soloman (20). The recurrence of glycogen in the vaginal epithelium accompanies the rapid alteration of the mucosa to the cornified adult type. The return of Döderlein flora and vaginal acidity is also noted The labia increase in size and the mons pubis takes on adult characteristics The cervix and uterus begin a rapid growth period and a slow change of the cervicouterine ratio is instituted. This ratio change is usually complete by the sixteenth to eighteenth years of life. Growth and deposition of fatty tissue in the breasts is also characteristic of this stage in the female reproductive cycle. In addition, during adolescence actual growth in body structure occurs. There may well be some synergistic action between the effects of estrogen and the pituitary growth factors upon the musculature and the bony structure of the female adolescent. Certainly there is a real relationship between growth and sexual maturation which is best illustrated by a comparison of data from girls of the same ages divided into two groups, those who have experienced sexual maturation and those who have not. Pryor (21) supplied the statistical data in this direction. Sexually mature girls grow an average of 10.64 cm. in height in eighteen months in contrast with an average of 9.38 cm. during the same time for girls of the same age who have not experienced sexual maturation. Greulich (22) has reported the development of certain skin glands, especially axillary and pubic, at the time of adolescence which, together with the spurt of hair development in these regions, is well known to be associated with adolescent change.

Innumerable other physical and psychic changes occur during this adolescent or growth period in the individual female. As adolescence draws to a close and the stage of sexual maturity is reached, we realize that the phase of activity of the life pattern is upon us. This activity normally culminates in reproduction.

Sexual maturity—pregnancy and postpartum involution

The active phase of the female reproductive life consists of repeatedly attempting to reproduce. Every fulfilled menstrual cycle marks a distinct failure of the individual woman to carry out her assigned sex activity—propagation of the race.

The basic endocrinology of the menstrual cycle has been discussed in Section 1. We should consider briefly here, however, the ageing or regressive factor that is probably primarily responsible for true postovulatory bleeding —the involution of the corpus luteum. Sexual maturity in women is basically marked by repeated ovulation. When the ovum is extruded from the follicle at ovulation, its demand on the follicle for sustenance ceases. The cells in the walls of the ruptured follicle apparently continue to store food because a marked accumulation of lipoid material appears. There is also a decrease in growth activity noted by basic cessation of cell division. Then the active phase of life of the corpus luteum, the production of progesterone, begins. In case the ova are not fertilized, the life span of the corpora lutea is relatively short. In the human ovaries, scars of old corpora lutea may be found for perhaps a year after ovulation. Their secretory function normally has at the most, a ten to twelve day span. The rest of the life of the corpus luteum is taken up with involutional processes. In case pregnancy does occur, the activity phase of the corpus luteum is prolonged for an indefinite period of time. It does not, however, approach the termination of gestation as a life span. The active phase of the corpus luteum is probably only three to four months. Certain it is that late in pregnancy the corpus luteum of pregnancy has ceased functioning, as negative bioassays at the time of cesarean section have repeatedly proven.

The short life span of the corpus luteum of menstruation, terminating in the processes of involution, is probably basically responsible for the onset of typical menstrual flow. At present, one of the most widely accepted theories as to the actual onset of postovulatory menstrual flow is that this flow is essentially progesterone withdrawal bleeding from a previously estrogen stimulated uterus. The tenets of this faith have been amply expounded by the contributions of the Smiths (23, 24).

We have discussed selected growth and involutional factors of the product of conception from its incipiency through the immediate postnatal period in Section 1. A brief consideration of the remaining pair of the triumverate of birth, uterus and placenta, is in order here.

The outstanding example of the growth period connected with pregnancy in the female reproductive system is found in the uterus. Eastman (25) tells us that the uterus is converted from a small almost solid organ 6.5 cm. long into a thin-walled muscular sac capable of containing the fetus and placenta and a large quantity of amniotic fluid. At the end of pregnancy it is about 32 cm. long, 27 cm. wide and 22 cm. deep. Its capacity has been estimated to be increased 519 times. This tremendous hypertrophy or growth period (34 fold increase, according to Reynolds (26)) terminates with the onset of the phase of activity. The assigned activity of the gravid uterus is, of course, the protection and ultimate delivery of the fetus and

placenta. Immediately following the termination of the period of growth and the phase of activity, involution begins in the uterus The uterus contracts immediately after the expulsion of the placenta to a solid mass of tissue which measures 4 to 5 cm. in thickness through the walls. It regains its normal size from six to eight weeks after delivery. The involution is carried on so rapidly that a uterus which weighs approximately 1000 g. at delivery, may weigh 500 g. one week later, and at the end of the second week 375 g., finally shrinking to the normal weight of 40 to 60 g. at the end of the puerperium. During the few weeks of the puerperium, when this greatest known example of atrophy in the human race is at its height, muscle fibers shrink to approximately one-tenth of their former size. The blood vessels also decrease in size but remain quite tortuous, and for this reason a previously pregnant uterus can usually be distinguished from a nonpregnant one.

It has long been known that the placenta itself ages and begins degeneration before birth. Loss of elasticity in the vessel walls, patches of necrotic tissue, fibrosis and other alterations similar to ageing changes have been described in placentas from normal pregnancies at term. This led to Warthin's (27) concept of the placenta—an organ which is derived from both maternal and embryonic tissues, yet has a definite life span which is limited by the gestation period. There is no question that the life span of the placenta can be continued beyond the expected period of gestation, as demonstrated by Snyder and Wislocki (28), who developed a second set of corpora lutea in the ovaries of the rabbit and succeeded in extending the gestation period for several days. Similar evidence has been noted in our own department in 3 cases of known intraabdominal pregnancy which were terminated by cesarean section at or near term, and the placenta allowed to remain in the abdominal cavity subsequent to the removal of the fetus. Active function of the placenta, in terms of measurable production of chorionic gonadotrophin and sodium pregnandiol excretion was present for at least three weeks postpartum. Despite these examples, it is essentially true that placental function, or the normal phase of placental activity, ceases at the time of delivery of the fetus. It is even postulated in several circles that the onset of labor is primarily the result of ageing and involutional changes in the placenta resulting in subsequent reduction in hormone production. Certain it is that this organ, whose growth period is as rapid as that of the fetus itself and whose period of activity consists primarily in providing a means of sustenance and growth for the fetus, begins involutional changes at a time when its full activity no longer is necessary for fetal growth.

The placental phase of activity is the most complex known to man. The placenta is without doubt rivaled only by the liver in complexity of

metabolism and multiplicity of function. Vosburgh, Flexner, Cowie, Hillman, Proctor and Wilde (29, 30) have recently made tremendous strides in answering the innummerable questions involved in the major subject of placental transfer, or fetal maintenance. Wislocki and Dempsey (31, 32, 33) have provided histochemical tools to aid in evaluating trophoblastic metabolism. The tremendous production of progesterone, estrogen and chorionic gonadotrophin are established facts due to the efforts of such workers as Jones, Delfs and Stran (34) and Venning (35).

It is an interesting commentary on the process of reproduction that the second stage of labor is concerned with giving separate life to the fetus, while the immediately following third stage of labor involves the separation and death of the placenta. Never were life and death more closely associated or more dramatically or graphically portrayed than in the intimate terminal association of involuting placenta and rapidly growing fetus. The former grows—is intensively active—and perhaps during the processes of involution is responsible for initiating that chain of events termed labor and which terminate in new life.

The growth, activity and involutional changes in the breasts during and after pregnancy must also be considered in this discussion of the functions of sexual maturity. Shortly after the first missed period the pregnant female may complain of tenderness and tenseness of the breasts. After the second month, however, the breasts begin to increase in size, and the period of growth is well under way. Not only does the breast tissue definitely increase, but there is a tremendous increase in blood supply, and a concomitant venous engorgement is soon noted. The nipples themselves soon increase in size, become more erectile, and during the fourth to sixth months of gestation produce the first signs of the physiological function—activity phase—of the breasts. This is of course the production of colostrum which has been aptly named the precursor of milk. Growth becomes negligible in the breasts during the last trimester of pregnancy, although in the terminal four to five weeks, a change to a more cylindrical shape is noted, and the nipples become even more prominent. One has the impression that this is an alteration of shape, or a redistribution of adipose tissue, rather than a continuation of the growth period.

Immediately subsequent to the delivery, the major activity of the pregnancy-influenced breasts comes into being. On the third or fourth day postpartum, the breasts suddenly become much larger and more tender. This is actually lacteal secretion, and the earlier production of colostrum is giving place to the life-sustaining production of mother's milk.

From a hormone point of view, the growth of the ductal system in the breast is probably the result of placental estrogenic hormone stimulation. According to Gomez, Turner and Reece (36) estrogenic compounds may

stimulate the pituitary to produce increasing amounts of duct-growth principle (mammogen one), while the growth of the lobule-alveolar system is brought about by a second mammogenic hormone (mammogen two). The production of this hormone is considered to be dependent upon stimulation of the hypophysis either by progesterone alone, or by progesterone and estrogen acting together. Suffice it to say that the growth period of the mammary gland during pregnancy is certainly dependent upon the action of the ovarian and placental steroids. These steroids may independently mediate the duct growth (estrogen) and the lobule-alveolar development (progesterone) of the breasts (Hisaw and Astwood (37)) or the growth may well be due to the interaction of the ovarian and mammogenic hormones as described above.

With the weaning of the baby, involution of the mammary glands incurs remarkable changes. Secreting alveoli shrink to insignificance and almost completely disappear. Only the main branches of the duct system persist. This is completely similar to the involution of the mammary glands in old age or following castration.

It is obviously necessary then for a spurt of growth to renovate the mammary apparatus before lactation will be resumed. Does this mean that these tissues, too, have a relatively short span of life and activity, a span extendable by increased function, but one which has definite limits none the less?

The Climacteric

The study of the female reproductive system during its fifth and sixth decades of life is of particularly challenging gerontological interest. It is during this time that the fourth great milestone of female life is permanently cemented into place. For most women, questions concerning the reproductive system will be forever after referred to as either "before or after my menopause." That the menopause represents a true change of life for most women is a fact which cannot be denied. Yet the mere cessation of menstrual flow is in most instances only a final link in a chain of events that may well have had its onset five to ten years previously.

The entire process of ovarian functional resolution and subsequent involutional changes in the pelvic viscera usually has its origin in the early forties. The terminal stages of these retrogressive processes may extend past the menopause and into subsequent senile atrophy of the pelvic viscera in the early or middle fifties. This involutional process with its accompanying vasomotor and psychosomatic complaints has been aptly termed the climacteric. This period of life is in truth a change, and with it we have marked the end of the two great phases of living, first of growth, and second of activity. For in truth, with the cessation of menstrual flow,

finis is written to the active phase (the processes of reproduction) of the female reproductive system. The third and last of the great triad of life, the processes of involution, now assumes dominance. Progress now is backward, and the end result is senility.

As has been previously mentioned in this chapter, some of the earliest signs and symptoms of ageing are demonstrated in the female pelvic viscera by the "premature" involution of ovarian function. It is strange that while other organs or other members of the endocrine system are functioning in a most satisfactory manner, ovarian function is the first to show definite retrogression. The subject of ovarian reserve becomes then of major moment.

Reduction of ovarian reserve as a sign of ageing

The term reserve connotes the extremely large factor of safety of function associated with many organs of the body, the prime example of which is the liver. The endocrine glands share strongly in this safety factor. Ovarian reserve simply means that the ovaries during normal periods of function are still not working to capacity even during their most productive periods. For instance, it has long been known that if one ovary is removed from an animal such as the rat or the mouse, the remaining ovary, which normally produces four or five eggs at an estrus period, will double its production to replace the function of the ovary removed; at least it does so in young animals. This phenomenon of compensatory hypertrophy of the remaining ovary was first termed follicularie constance by Lipschutz, Wagner and Tamm (38) in 1922. In reality the determination of work hypertrophy by the remaining ovary was first recorded by Hunter (39) in 1786 subsequent to his famous hemicastration of a young sow. Wiesner (40), in an important report, states that after an ovary is removed from old animals there is not the amount of compensatory hypertrophy one would expect from the experimental work with young animals. This might be interpreted as demonstrating that the ovary has lost some of its productivity—that is, its factor of safety is reduced with ageing. We have many clinical examples of the compensatory hypertrophy of the remaining ovary of a woman in her twenties or early thirties subsequent to the removal of one ovary at the time of surgery. In our own laboratory we have followed several patients by means of Shorr stained vaginal smears (41) which upon interpretation suggest repeated and true ovulation subsequent to such surgery as the removal of an ovary containing a dermoid cyst. The hemicastrate syndrome which such an operation develops is best explained by the following example. If a young woman of 20 years should have one ovary removed, her anticipated menopause would then be at approximately 35 years of age, rather than the normally anticipated 50 years. Thus the

removal of one ovary would literally age the remaining ovary at twice its normal rate.

While we have had no experience with lack of hypertrophy (in terms of work production) in the one remaining ovary of a woman of the age of 40 or beyond, follicular cysts have been seen to develop most readily in such a situation. It could be argued in this instance that no true compensatory hypertrophy had taken place. However, the possibility should also be considered that the stimulus (increased gonadotrophic stimulation) to replace the function of the lost part was present but that the ovary itself, due primarily to an already established lack of reserve at the more advanced age level, could not meet the demands that were placed upon it.

Another purely clinical and yet important observation in the field of ovarian reserve is the well established syndrome of the woman 40 to 45 years of age who visits her physician with many of the symptoms associated with the terminal stages of the climacteric, such as occipital headache, nervousness, irritability and even occasional hot flushes. This individual may still be menstruating regularly. Vaginal smears or rectal temperatures may well lead us to believe that she is ovulating. Examination of the smears and clinical examination of the vagina reveal, however, a definite reduction in the amount of cornification present. Perhaps a clinical estimation of 65 to 70 per cent stimulation of vaginal mucosa would best fit this picture. This particular situation is usually true in the type of individual who, in her early forties, is demanding much more of her physical and mental being than would be usual for that age group in the normal female existence. For example, let us take the advertising executive whose high-powered day is terminated with a rush home late in the afternoon to take care of the demands of husband and family. In this instance one feels certain that, although the patient is ovulating with significant regularity, the ovarian reserve has been more than used up by the excessive demands such an individual places on her general body metabolism. A woman in this category is certainly well along in her climacteric even though she is still exhibiting regularly recurring vaginal bleeding.

The menopause

The true menopause, which specifically means cessation of menses, has been bent by more or less common usage to cover the entire life period that has been previously ascribed to the term climacteric. We should use the term menopause, however, in its purely definitive sense and describe it primarily as the line marking the termination of stage two and the beginning of stage three in the process of sexual ageing. As a rule in this country menstrual bleeding ceases between the forty-fifth and the fiftieth year. Occurrence of the menopause earlier than the age of 40 is called premature,

or precocious, menopause. A reverse, or continuation of flow past the age of 55, is seen much more frequently. Hamblen (42) takes issue with the previously accepted concept that a woman who has a delayed menarche usually has an early menopause. In doing so, he quotes data on women in Great Britain (43) to substantiate his contention. The average age of menopause for these women who experienced the menarche at 14 years of age was found to be 47.3 years, whereas for those whose menarche occurred at 18 years, the average of menopause was 47.5 years. It is apparently more credible, as noted by Hutton (44), that an early menopause may occur more frequently due to the intense artificiality of both mental and physical existence in the type of life we are now leading. He draws examples from women who enter such demanding careers as business or a profession.

The basic and underlying cause for the menopause is, in all probability, the failure of the ovaries to respond to pituitary stimulation. Certain it is that the first evidences of ovarian insufficiency from a completely hormonal point of view are failure of ovulation, and of course, the concomitant failure of corpora lutea formation and progesterone production. Without satisfactory progesterone production, a definite lag occurs in the mutual stimulatory effect between ovary and the anterior lobe of the pituitary. The ovaries continue to respond to the follicle stimulating hormone from the pituitary. This hormone is produced in even greater amounts than in the childbearing age as the result of a basic physiological urge to return a failing ovarian function to normal. However, after a significant period of time, even the ability of the ovary to respond to the follicle stimulating hormone fails, and vaginal bleeding no longer occurs despite high levels of measurable follicle stimulating hormone in the urine.

This one great change in responsiveness of the ovary to extraneous stimulation is the first major sign of ageing in the female endocrine system. If we could find the answer to the great question of why the ovary cannot respond to even excessive amounts of gonadotrophin stimulation, we might well have gone a long way towards solving the basic problems of degeneration or involution. One basic suggestion supported by many clinicians is that the ovary is prematurely aged or worn out. It is possible that the tremendous activity phase of normal ovarian life may be a striking adjunct to its questionably premature senility. The pituitary gland also shows evidence of the reaction change in its basic physiology after it first loses the stimulation of progesterone production and secondly the stimulation of estrogen production. Its own cyclic production of first follicle stimulating and then luteinizing hormone is lost, and it becomes uniphasic in gonadotrophin production instead of biphasic, producing only follicle stimulating hormone. This it does in excessive amounts. The production may well have returned to normal before vaginal bleeding actually ceases, as it must be

remembered that true ovulation may fail for as long as eighteen months to two years prior to the actual menopause. Generally though, this challenge actually results in a state of hyperactivity for the pituitary which probably also involves thyrotrophic and adrenotrophic hormones in addition to the excessive output of follicle stimulating hormone. However, *deprived of its basic ovarian stimulation*, the period of pituitary hyperactivity may well cease within one to five years subsequent to the menopause. Although satisfactory results in terms of evaluating the postmenopausal period of the female life from a gonadotrophic point of view are only now becoming available, the impression is gathered that the hyperactive period of the pituitary seldom lasts longer than five years

Symptoms of the climacteric

A tabulation of symptoms for both men and women by Werner (45) shows psychoneurotic and vasomotor instability to be far in excess of any other combination or concentration of symptoms. On the other hand, variations of major importance are noted. One of the most prominent of the changes associated with the climacteric is, of course, the bleeding change. Vaginal bleeding rarely ceases abruptly Usually due to anovulatory cycles, the bleeding may occur more frequently, perhaps at twenty-one day intervals, for several months prior to the occasional omission of a period The amount of menstrual flow is generally reduced, and not infrequently, the flow is a watery, pale red color rather than the true dark red menstrual bleeding. Usually patients, having missed a period, will continue in this vein for a year to eighteen months skipping occasional periods until they are menstruating but 3 to 4 times a year. It may then take one to two years before all vaginal flow ceases. *It is of major importance to remember that persistent spotting or bleeding more than a year or eighteen months after apparent cessation of regular menstrual flow should be carefully investigated with the possibility of cancer of the pelvic viscera constantly in mind.* In addition to the ultimate cessation of menstrual flow, significant changes are noted in the size of the uterus and cervix and the stimulation thickness of the vaginal wall. The uterus becomes much smaller, and the cervix, as the period of amenorrhea continues, shrinks into almost buttonlike size. The vaginal wall becomes thin, light pink in color and has a glazed appearance which gives the impression that one can almost see through the epithelial lining. The rugal pattern almost completely disappears under continued amenorrhea. The fatty tissue deposition in the mons and the major labia also disappears and pubic hair becomes thin and coarse in two to three years after the cessation of menstrual flow.

There are innumerable other less direct effects of climacteric change which are of real interest. Sevringhaus (46) has pointed out that weight

changes, skeleton modifications, and alterations of the skin constantly accompany the advance of the climacteric. Since there is a well established simultaneous pituitary activity concomitant with changes in weight and skeleton, the pituitary has been frequently cited as a main source of the climacteric symptoms. This has never been proved satisfactorily.

Of major import are the subjective symptoms that are associated with the slow progress of the climacteric. Hot flushes, occasional headaches, usually in the occipital region, and periods of dizziness are frequently concomitant with a reduction of estrogen production of clinical magnitude. There are, in addition, many subjective symptoms such as increased irritability, nervousness and emotional instability, which includes such corollaries as memory impairment, easy fatigability, periods of depression and increased difficulty of concentration. Primarily these symptoms seem to be associated with a general clinical impression of a basic loss on the part of the patient of a sense of well-being. This is probably the primary psychological change associated with the climacteric.

An excellent warning is sounded by Buxton and Engle (47) when they point out that the climacteric has many facets, estrogen depletion being but one of these. It is occasionally a very difficult condition to diagnose accurately, and certainly may be a confusing one to treat. Frequently the menopause is accused of being the etiological factor in any pathological situation occurring in a woman over 45, whereas the symptoms may be due to the insidious onset of serious disease. It is inevitably true that the laity as well as the medical profession are all too free to hang a diagnosis of the climacteric syndrome on practically any physical or emotional disability or distress that occurs between the ages of 45 to 55. The diagnosis of menopausal syndrome is a very easy one to make, but at times a most difficult one to substantiate.

Castration syndrome

Surgical removal of the ovaries or complete destruction of ovarian tissue by x-ray therapy is followed by a premature menstrual period, usually within five to eight days after the operation or cessation of treatment, and subsequent to this a complete cessation of menstruation ensues. This might in truth be called operative or x-ray menopause as it is similar in many respects to the naturally occurring one. The uterus, mammary glands and vagina atrophy after oophorectomy in young women just as they do after a normal menopause, although the degeneration progresses more rapidly in the younger age groups. There is usually decrease or loss in sex drive, but in some cases a compensatory increase in sex interest above normal limits has been noted.

Hot flushes appear within two to six weeks after oophorectomy and other

symptoms associated with the normal menopause may occur with even more marked severity. These are primarily symptoms of nervousness, irritability, emotional instability and occipital headaches. Since these symptoms occur in young women, it is more obvious that they are not dependent on the inadequacy of other systems, the vascular or nervous for example, but result from lowered functions of these systems due to removal of stimulative impetus.

Corroborative evidence that the removal of estrogenic hormones and the associated hypertrophy and increased activity of the pituitary gland are responsible in the main for the symptoms associated with the climacteric syndrome is found in the now well established clinical entity of replacement therapy. By this we mean the administration of sex steroid preparations to a patient who is suffering objective or subjective symptoms of the climacteric and thereby obtaining relatively quick and satisfactory relief of the symptoms noted. Werner and Collier (48) were the first to report the production of menstrual flow in patients who had been previously ovariectomized. There have been many instances of successful replacement therapy with ovarian hormones since this first reported success. It is also interesting to note that as clinically adequate estrogen levels are obtained, the measurable gonadotrophin output in the urine precipitously diminishes.

Not only can vaginal bleeding be restored, but as suggested, a considerable alleviation of climacteric symptoms can be obtained by adequate and intelligent handling. Sevringhaus (49) states, "These vasomotor and psychic symptoms may occur in women before the menopause, but the significant thing is that after castration of a woman who has no other disturbances, these are the symptoms reported. They appear frequently in spontaneous menopause. There is, conversely, the experience that all these symptoms can be evaded and usually completely relieved by the use of an adequate dose of estrogenic chemicals."

Since many of the climacteric symptoms are subjective, the question arises as to what extent psychological factors may enter into the results reported. The difficulty of adequate controls for clinical experimentation is often cited. To meet this excellent objection, periods of treatment with ovarian hormones have been alternated with trials of similar materials which do not contain the hormone. This method of placebo therapy was first entertained by Pratt and Thomas (50) and suggests an adequate way to control clinical therapy observations. There can be little doubt that merely the fact that the doctor is prescribing something for the severe symptoms of the climacteric may help many patients. When beneficial results are obtained during injections with placebos, it must be admitted that the effects are primarily psychic. On the other hand, when treatment with estrogenic hormones alleviates conditions, and when later, following

substitution of a placebo without the patient's knowledge, there is a recurrence of symptoms, evidence for the effectiveness of hormone therapy is obvious.

It should be borne in mind constantly that in many instances menopausal symptoms are primarily psychic in origin, and it has been suggested by Buxton (51) that about 50 per cent of the cases of the climacteric syndrome can be relieved completely or to the extent of clinical satisfaction by simply the administration of mild sedatives. It is a safe clinical rule in treating patients with climacteric symptoms to use the least possible medication adequate to produce the best possible results.

Endocrine hypofunction and premature ageing

In addition to the evidence present of a premature climacteric syndrome as an immediate corollary to surgical or x-ray castration, we should consider briefly the state of hypoendocrinism which will simulate or actually produce premature ageing. Either through disease, inadequate nutrition, or excessive or deficient pituitary secretion, hypogonadism contributes its part to the collective principles for interpreting ageing of the reproductive system. The condition of primary hypoovarianism, in which the ovaries for some reason fail to produce adequate levels of sex steroids, is well recognized. Hereditary factors may be responsible for such conditions, for certain endocrine states are genetically determined, as was suggested by Stockard (52) in his experiments with the inbreeding of dogs.

If the ovaries are involved secondarily, however, the supporting secretions of the pituitary and of the thyroid must be considered as possible etiological sources for hypoovarianism. Since hypopituitary effects upon the ovary can be reproduced experimentally by hypophysectomy, there has been much experimental study in this direction. Although the anterior pituitary has a large degree of the safety factor—excellently demonstrated by Rogers' (53) experiments in rats—that has been previously predicated for the ovaries, satisfactory anterior pituitary secretion is still necessary for the late growth of ovarian follicles, ovulation and the formation of corpora lutea. In this connection Simmonds' disease, cachexia hypophysea, has a bearing on the subject of ageing of the female genital system. The most important symptoms of this disease are premature ageing, associated with rapid atrophy of the genital organs, regression of the secondary sex characteristics and loss of hair. The disease is not frequent, but its incidence is highest in comparatively young women. It is due to atrophy of the anterior pituitary and certainly is similar in many respects to the castration syndrome which arises subsequent to surgical or x-ray deactivation of the ovaries.

The converse hyperpituitary conditions are readily reproducible ex-

perimentally. Precocious puberty has been cited. Smith and Engle (18) in 1927 induced ovulation of as many as 48 and 63 eggs in the mouse by increasing the anterior pituitary hormones

The thyroid also has a gonad supporting function, as is shown by the fact that thyroid therapy may frequently be effective in alleviating amenorrhea and sterility even in cases where the basal metabolism may not be particularly low, if the situation is not complicated by other factors. It is logical then to suppose that with decreased thyroid activity as old age advances, there may be a decreased endocrine support from this gland to ovarian function.

Suffice it to say, there are innumerable symptoms of the climacteric, both of psychic and somatic origin. There are as well retrogressive changes in the breasts and pelvic viscera and variations in general body physiology, in addition to such diverse effects as widespread skeletal, weight and skin alteration. All of these changes are harbingers of a new era in the female life. The primary period of growth has passed, the multiple phases of mature sex function and activity are behind her, and slowly but surely, the evidence is accruing that the third division of the triad of female life, encompassing the processes of involution, has now become of major importance and will continue to rule the body physiology through the stage of senility and actually for the rest of the individual's life.

Senility

One of the most interesting practical considerations of the absolute menopause, and the subsequent postmenopausal atrophy and shrinking of the pelvic viscera, is that these involutional effects often favor complicating infections. The atrophy associated with the removal of estrogen from the circulating blood stream affects not only the uterus, tubes, ovaries, vagina and vulva, but the mammary glands as well.

The extent to which atrophy of the ovary and the uterus may proceed is only fully realized when a careful search is made at autopsy or during the course of seventh or eighth decade surgery. The ovaries of a 70 year old woman are found to be nothing but small fibrous bits of tissue, and the uterus is extremely small and fibrous in character. A one to one ratio generally exists between the cervix and uterus at this time. Infection of the atrophic genital organs may occur and frequently the infection becomes chronic. There are now many reports in the medical literature of cases in which treatment by estrogenic hormone has started growth of vaginal tissues and restored them to a nearly normal mature condition. The treatment often results in clearing up chronic genital diseases both atrophic and infectious in origin. There are, in addition, many subjective complaints such as loss of libido and the inability to carry coitus to satisfactory con-

clusion due to intense irritability of the vulva, vaginal outlet or the vaginal walls themselves. The very thin and atrophic vaginal wall has returned to a state similar to that seen in a youngster 5 or 6 years of age. For that matter, one of the first suggested uses of estrogens to combat infection in this type of atrophic vagina was in the treatment of gonorrheal vaginitis in children. Lewis (54) suggested that the vaginal mucosa be built up under estrogenic stimulation to aid in fighting this disease. Davis (55) and others followed Lewis' lead in the use of estrogen as it applied to the treatment of atrophic conditions and steroid replacement has become a commonly accepted method of treatment in the postmenopausal life.

Under the stimulus of estrogen, the very thin vaginal epithelium grows to a thick healthy membrane, glycogen appears in the vaginal epithelial cells and the reaction of the vagina changes from an alkaline to an acid one which is unfavorable to the life of infecting organisms once the pH has been lowered beyond a level of 5. Treatment by local applications of estrogen is usually followed not only by relief of symptoms, but actual negative bacterial cultures from the vagina. This treatment is of course particularly effective if it is associated with any of the controlled pH vaginal jellies that are on the market. The rationale behind this therapy is primarily one of using an acid jelly of a controlled pH of 4.5 to maintain vaginal acidity until the time when the vaginal mucosa is able to reach a sufficient stage in cornification to begin to slough the exterior cornified cells into the vaginal canal. These cells are filled with glycogen, and in the process of degeneration liberate lactic acid which in turn aids in supporting a low vaginal pH.

A major drawback to this type of replacement therapy, when employed intermittently, is the fact that discontinuance of postmenopausal treatment is followed by a return of the previous atrophic condition of the vagina. The optimum type of therapy is to supply the patient with that amount of estrogenic stimulation which will provide vaginal cornification to the degree necessary to protect against infection and which will not be sufficient to stimulate the uterine endometrium to build to the point of breakdown and sloughing. Work in this direction will be taken up in Section 5.

Hypertrophic and neoplastic diseases

Simple hypertrophic diseases seem to occur frequently after the menopause. The ovaries may become cystic and such cysts may persist for a considerable length of time and in some instances secrete undue amounts of estrogen. These cases may be accompanied by such secondary sequellae as uterine hemorrhages or blocked or distended mammary ducts leading to mastitis. Usually these conditions clear up spontaneously or will subside

subsequent to depressive doses of estrogen and testosterone or x-ray therapy. It should be noted parenthetically that ovarian tumors which actively secrete estrogens (granulosal cell tumors) may reproduce the picture described above to the last detail. Care should be taken in dealing with this situation as such tumors undergo malignant degeneration in approximately 30 per cent of the cases according to Novak and Brawner (56).

Neoplastic diseases, such as cancer of the mammary glands, the cervix and the corpus, have their highest incidence during the fifth and sixth decades, primarily associating themselves in concentration with that ten year period immediately before and after the cessation of menses. Macklin (57) has placed the incidence of female reproductive organ (including breast) cancer at approximately 20 to 30 per cent of all cancer. Why the highest incidence of genital cancer should occur within a ten year period associated with the cessation of the menses is a difficult question. Animal experimentation has offered a suggestive answer to the problem by pointing a questioning finger at the possible carcinogenic effects of sex steroids.

The foregoing discussions have developed the thesis that the spurts of growth in the female genital organs are due to the action of the estrogenic hormones. Genital cancer is really a new, although atypical, growth of cells in the genital organs. Those who side wholly or in part with a belief of the carcinogenic effects of steroid hormones easily hark back to the work of Strong (58) in 1936 with his inbred strains of mice. Rapidly growing malignant cancer of the mammary glands in these inbred strains of mice kills the animals in a month or six weeks after the tumor first makes its appearance. Over 80 per cent of the females of this strain die after reaching the age of $1\frac{1}{2}$ years The males do not have mammary cancer unless stimulated with heavy dosages of estrogen. When they are feminized to the extent that their mammary tissues grow, cancerous growth develops. Lacassagne (59) was among the first to prove this point. It must be constantly recalled, however, that animal experimentation cannot be translated into human terms. In addition, it must also be noted that a genetic factor for cancer certainly may be involved in these mice. Following the work of Danforth (60), it has become apparent that some structures do get their first directional impulses genetically. Then the course of development may be continued or changed by the action of hormones. It is difficult, of course, to determine in many instances where the genetic influence stops and the hormone influences take control. Apparently it is possible to produce genital cancer in certain strains of inbred mice, where such cancers were infrequent, under long continued hormone treatment, but Allen and Gardner (61) were unable to derive any absolute expression in the belief of the carcinogenic action of estrogenic compounds as a result of their work. Cancer is an uncontrolled growth. Just what sets these cells free

from the restraint of the growth stimuli which control other tissues of the ageing body is still the major unsolved question in cancer research. Basically speaking, they are young cells in a period of growth, while generally speaking, the host site in the female generative tissues has shown significant evidence of being well involved in the innumerable processes of the degeneration and involutional periods. In the sex hormone, however, there unquestionably exists a powerful stimulator for growth of the genital tissues. Many experiments are in process to test the question "Will long continued or abnormally high levels of estrogen produce excessive, atypical, abnormal or perhaps cancerous growths?" Some of the work in this direction is presented in the next section.

Senility is an all encompassing term used to denote both mental and physical involution from the active fifties and sixties to the infirmities of the seventies and beyond. The changes in the female pelvic organs past the age of 60 years are actually minimal but are important. The atrophic diseases of the vulva such as simple kraurosis or leukoplakia are now in the foreground. Actually a great variation in the amount of vulval atrophy in the 70 year old female is noted. In some instances the labia have practically disappeared due to fatty tissue wastage, while in other cases, although atrophy is obviously present, relatively normal appearing vulval structures are maintained.

Cancer of the vulva should also be mentioned as it has its highest incidence in the ten year period from 61 to 70 years according to Taussig (62). Since approximately 1 out of every 20 cases of pelvic viscera cancer in the female is vulval in origin, any nodular growth or persistent area of ulceration on an atrophic labia should be examined with suspicion.

We have obviously reached the stage in our discussion where processes of involution are alone considered. Growth and activity were left with sexual maturity. While one cannot turn back the hands of the clock, most clinicians believe that a great deal may be done to preserve some degree of physical and mental function and thereby provide the necessary ingredients for a happier and more useful twilight of life. Gerontology is dedicated to this aim.

Experimental Evidence of Senile Pelvic Viscera Regeneration

The female sex hormones have been used for many years in the treatment of symptoms which occur due to ovarian deficiency, as has been described previously in this chapter. Endocrine replacement therapy has been given for the most part to patients having symptoms during the natural climacteric or from distress brought about subsequent to an artificial menopause. Until the last six years very little study had been made of the effects of replacement therapy in the aged woman many years past

her menopause. There is no particular reason for giving sex hormones to aged women in so far as producing relief from the climacteric syndrome is concerned, for such women usually have none of the usual symptoms. However, there are excellent reasons for wanting to know what effect this type of substitution therapy may have on the organs of reproduction in part, on the systemic organs in their entirety and on the body as a whole.

The prime result of rejuvenation of pelvic viscera under the influence of sex steroids has been to demonstrate a reversal of the inevitable involutional and degenerative processes of ageing. These experiments afford the opportunity of extensive study of the heretofore generally unexplored processes of regeneration in the ageing individual.

The hazards of prolonged treatment with sex hormones may be of considerable import Such well recognized clinicians as Fluhman and Stephenson (63), Crossen and Hobbs (64), Smith (65), and more recently Gusberg (66) have sounded repeated warnings of the possible carcinogenic action of the long continued estrogenic stimulation of the corpus uteri. They consider hyperplasia of the uterine endometrium a possible precursor of adeno-carcinoma in this site.

There is no question concerning the clinical observations reported. It is interesting to note that these observations primarily were made in the presence of long range *unopposed* estrogenic stimulation of the pelvic viscera. If there is a carcinogenic effect contained in estrogenic compounds, it may well be that the long range unopposed influence of estrogen may allow this carcinogenic action to obtain dominance. It was with two basic thoughts in mind that the pelvic rejuvenation work to be discussed was instigated. The primary interest was to see what results could be obtained in rejuvenation work with senile pelvic viscera, while the secondary interest involved determining whether long range estrogen administration could be carried out under controlled conditions that would prevent unopposed estrogen being exhibited for long lengths of time. So far, one can state

the paragraphs below

In order to avoid the possibility of endometrial hyperplasia subsequent to long range estrogen therapy, the major policy has been to oppose the effects of estrogen at cyclic intervals by the exhibition of either progesterone or testosterone, by the removal of estrogenic influence at certain periods of time or by concomitant estrogen-testosterone therapy. Many research

patients have been placed on a dosage of 2 mgm. of estradiol benzoate a week and have been maintained on this dosage for at least five, and in some instances six, years without any break in the biweekly 1 mgm. injection.

The first method of therapy involves the use, at cyclic intervals, of varying dosages of progesterone (67, 68) provided in quantities sufficient to insure breakdown and slough of the estrogen stimulated endometrium. A second method of estrogenic opposition has been provided by the cyclic monthly administration of androgens (69). Testosterone propionate, when given in satisfactory concentration, produces luteal effects on the uterine endometrium which ultimately leads to a breakdown and shedding of the endometrium associated with androgen withdrawal bleeding. The process is essentially similar in physiological consideration to that described for progesterone withdrawal in Section 1. A third method is to discontinue the maintained estrogen levels at regular cyclic intervals to allow estrogen withdrawal bleeding. This method provides for, in effect, a brake against long continued unopposed estrogen dominance by means of the tissue effects of estrogen itself (70). A fourth method, and that with the most possibilities, is to try to avoid uninterrupted, long range, tissue dominance of the constantly maintained estrogen dosage by concomitantly treating the patients with testosterone (71). In other words, this plan of therapy is to parallel both the long maintained estrogen influence with the equally long maintained testosterone influence. The difference between methods four and two is that in method four the testosterone influence is constantly maintained, while in method two the testosterone influence is purposely cyclic in character. This last method of treatment recalls the use of a similar combination of drugs in the treatment of symptoms of the climacteric by such men as Geist and Salmon (72) and Kurzrok and Rothhart (73).

In the admittedly small series under observation (some 50 patients) for a period of five years or better, there has been no demonstrable development of carcinoma of the cervix, corpus or ovary, while under the above types of controlled replacement therapy. Our primary purpose, then, in the controlled opposition regime, has been to avoid the development of endometrial hyperplasia. This has been successfully carried out by not allowing a condition of unopposed estrogen influence to exist for any significant period of time.

In terms of tissue regeneration, some of the results obtained have been of special interest. Water balance and tissue fluid regulation are recognized as extremely important factors relating to causes of ageing. Estrogen certainly plays a part in control over the concentration of tissue fluids in the female genital organs. The atrophic uterus contains very little water with the cells packed tightly together. Yet within a few hours of injection



FIG 4 (125 ×) Estrogen stimulation of stroma in early proliferative phase of the glands. Note the cystic gland.
FIG. 5. (175 ×). See legend for figure 6

6

7

Figs. 6 & 7

of varieties of estrogenic hormone in the rabbit there is a definite increase in blood supply and in amount of tissue fluid to the endometrium and muscularis of the corpus. Within two weeks the connective tissues are flooded with fluids and become spongy and edematous. Cell division follows soon after or accompanies these changes. It is of interest that similar effects have been produced by estrogens in the sexual skin of monkeys and by



FIG. 8. (105 ×). Endometrial biopsy taken on the eighth day of therapy from a patient receiving 50 mgm of testosterone propionate for 10 days Note the marked subnuclear vacoule formation in almost every gland, with migration of nuclei toward the lumina

male sex hormones in the cock's comb. These effects were described in 1939 by Allen, Hisaw and Gardner (74).

Figures 4, 5, 6 and 7 show the effects first of estrogen and then of super-

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[illegible] endometrial glands. Note the stromal

benzoate a week for 4 weeks.

FIG. 7. (100 ×). A biopsy that was obtained soon after the onset of bleeding in a patient who had received 5 mgm. of progesterone a day for 6 days in addition to a constant estradiol maintenance of 2 mgm. a week.

imposed progesterone on a basically estrogen stimulated endometrium. Of particular interest is the stromal edema and the extravasated red blood cells in the tissue—graphic evidence of increased tissue fluid in the uterine endometrium under the influence of these hormones. The activity phase of the rejuvenated endometrial glands (secretory activity under progesterone influence) should also be noted.

Figure 8 shows the effect on an endometrium well stimulated with estrogen of the opposition provided by the cyclic exhibition of testosterone. Again tissue edema and secretory activity of the glands may be demonstrated.

Further studies are underway at the moment to determine the effect of these hormones not only in the senile uterine endometrium, but in the muscularis, cervix, vagina and, for that matter, all of the tissues and organs of the body. As autopsies are now providing tissues for extensive microscopic examination, we may in the reasonably near future have even further evidence of tissue regeneration in the pelvic viscera. As an example, in some of the sections taken at autopsy from patients dying of natural causes after four or five years of therapy, there is now unpublished evidence to suggest decalcification of small and medium sized blood vessels in the myometrium together with a vast increase in the growth phase of the medial layer in these vessel walls.

Suffice it to say in brief resumé that the work in progress with senile individuals in terms of long range sex steroid replacement has approached the stage where we can say categorically that the endometrium and muscularis of the corpus, together with the vagina and the cervix, undergo regenerative changes. They demonstrate a new period of growth and selected examples of a renewed activity phase. These results have been obtained by primary, long range administration of estrogen under controlled conditions of cyclic opposition provided by other sex steroids, as has been described. The field is new and exciting, and the work is in its infancy.

Summary

We have considered the great triumverate of ageing: periods of growth—phases of activity—processes of involution in relation to the cardinal stages of life.

It is important to realize that the factors for ageing are inherent in the individual reproductive cells. Prior to the consummation of conception, there are examples of all members of the triad in the life cycles of the follicle cells and polar bodies that are intimately associated with the period of growth of the ovum.

Shortly after birth, the female reproductive organs show activity in breast and cervical gland secretion, involutional changes in uterine bleeding and vaginal, cervical, uterine and breast regression from the growth influence expressed by the maternal steroid levels.

Adolescence, the true growth period of the human female, also has clearly marked phases of activity and processes of involution. Ovulatory cycles now provide marked secretory activity, and, with progesterone withdrawal, cyclically demonstrate the extreme involutional processes that terminate in monthly vaginal bleeding. Nevertheless, this is a period of great growth, not only of the reproductive organs, but of skeleton, muscles, nerves and other tissues that compose the body organs and support their functions in the adolescent girl.

With sexual maturity we move into the greatest activity phase of female life. Inevitably, this is associated with reproduction—the ultimate expression of female sexual maturity. Yet, we must also be cognizant of great periods of growth and severe processes of involution which run as constant companions to the phases of activity. The carrying and delivery of the child, together with placental maintenance during fetal life, and breast support in the neonatal period are prodigious examples of activity. However, the growth periods of uterus, placenta and breast with their subsequent startlingly dramatic processes of involution are of equal interest and importance.

With the climacteric and its major landmark, the menopause, we reach the end of the close interdependence between growth, activity and involution. Growth and activity cease to play major roles in the physical being as the ovarian economy is destroyed and ultimate involution sets in. Reduction of ovarian reserve is the first general sign of this divorce of dependent cooperation, but such untoward states as ovarian hypofunction or premature castration provide isolated screenings of the events to come.

Slowly involution moves toward the ultimate—senility. Growth periods do occur, but many times they represent unfortunate and abnormal tissue changes, as the sufferers from hypertrophic or neoplastic disease of the female reproductive organs will freely testify. Activity phases are harshly reduced in efficiency to bare physical maintenance levels.

It is obvious then, that of the three great forces of physical life—growth, activity, involution—ultimate dominance must be accorded to the greatest and most inevitable force—involution. Thus we age.

In revising this chapter on the ageing processes of the female reproductive system, the author has pirated freely from the word and thought of his predecessor, Dr. Edgar Allen. To the memory of this esteemed investigator and gentleman, this work is most respectfully rededicated.

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26

MALE SECONDARY SEXUAL ORGANS

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With the increased knowledge in the field of endocrinology during the past decade, many organs and structures have been shown to be in part or in whole dependent on the hormones generally associated with maleness, that is, the androgens. The male secondary sexual organs will be considered in this chapter as including the prostate, seminal vesicle, vas deferens, and the breast. Because of the limitation of exact knowledge concerning changes with age in most of these organs, only the prostate will be discussed.

PROSTATE

Development of the prostate

The prostate gland is formed at about the twentieth week of life as a number of solid evaginations from the posterior and lateral walls of the urethra (1). These anlagen develop in both the male and the female embryo, but only reach their fullest development in the male. In the female, the glands remain vestigial in the wall of the urethra or in the urethrovaginal septum (see below).

Neonatal changes in the prostate

At birth the prostate in the male infant is a well developed structure and measures approximately 1 cm. in the three diameters. For a period of from seven to ten days after birth there is slight hyperplasia of the glandular epithelium and a conspicuous metaplasia of the urethral and ductal epithelium (2). These histological features regress and within two to three weeks after birth the acini and ducts are lined by a low cuboidal or stratified epithelium without evidence of secretory activity. It has been generally assumed, and probably correctly, that these neonatal changes in the

prostate are the result of stimulation by the estrogenic hormones carried to the infant from the blood of the mother (3). The changes are similar to those induced in monkeys by injection of estrogens (4). There are similar evidences of secretory activity in the breasts, more often in the male infant than in the female infant (5). The breasts are large, firm, and on section dark red in color. At times a small amount of a colostrum-fluid may be expressed from the nipples.

Female prostate

In all women there are small evaginations along the posterior wall of the urethra, but in 25 per cent there is a true prostate in which the glands penetrate the muscular wall of the urethra and are located in the tissues of the urethrovaginal septum (6). Nothing is known concerning the changes of these glands with age, but there is some clinical evidence to indicate that their presence may play an important rôle in the establishment of a chronic inflammation of the urethra (7). It is possible that infection of the female prostate is responsible for some of the cases of incontinence and irritation of the bladder neck in women. Under certain abnormal hormonal states, and in pseudohermaphrodites, there may be a fuller development of the female prostate (8). By comparison of the anatomical location and relation of the female to the male prostate, it is at once apparent that the two are not identical. The female prostate corresponds only to the lateral and middle lobes of the male prostate. The posterior lobe, the ducts of which empty distal to the verumontanum, is not represented in women. This analogy is further confirmed by a study of the prostate in pseudohermaphrodites (9). This fact is of considerable importance in an evaluation of the etiology of benign hypertrophy of the prostate, because this disease involves only that part of the male prostate which is represented in both sexes, that is, the ambisexual part. Experimental studies in animals fully confirm the observations in man. In female rats the injection of the dione derivatives of the androgens brings about hyperplasia of the female prostate in from 25 to 50 per cent of animals (10–12). This organ, developed under the influence of hormones, is entirely comparable with the male rodent prostate.

Morphology of the prostate in adults

A full understanding of senile involution of the prostate is dependent upon an exact knowledge of the structure of the gland during young adulthood. At puberty the small firm prostate with inconspicuous epithelium and no secretory activity becomes a large, well developed structure (3). The stroma consists of an equal mixture of fibrous tissue and smooth muscle. The muscle is arranged about the glands as a sling, so that con-

traction of it would result in pressure on all parts of a single acinus. The glands are typical tubuloalveolar structures and may be readily divided into five lobes. The posterior lobe is that part which is posterior to the urethra and the deferential canal. The ducts of this lobe empty into the posterior wall of the urethra, distal to the verumontanum. The middle lobe consists of those glands between the urethra and the deferential canal, and the ducts empty into the posterior wall of the urethra proximal to the verumontanum. The anterior lobe is a vestigial structure, and is represented by only eight to ten acini, the ducts of which open into the anterior wall of the urethra. The two lateral lobes include all those glands, the ducts of which have an orifice on the sides of the verumontanum. Aside from the atrophic anterior lobe, the structure of all of the lobes is identical. The epithelium consists of two layers. The luminal cells are tall columnar, with basal, round, moderately chromatic nuclei. In many cells the cell membrane toward the lumen is inconspicuous or absent, and the cytoplasm is apparently pouring out into the lumen as secretion. On the basis of this histological appearance it has been assumed that secretion by the prostate is of the apocrine variety. The basal layer of cells is at times incomplete and consists of flattened or cuboidal cells with small, round, chromatic nuclei. The basement membrane is represented by a narrow layer, from 7 to 10 microns in thickness, of homogeneous acellular material, staining like collagen. Throughout the stroma, especially about the ducts, there are numerous elastic fibrils. The blood supply is dual, termed an outer and an inner circulation (13). The recognition of this is important in an evaluation of the theory of the etiology of benign hypertrophy based on arteriosclerosis of the outer circulation. The blood vessels penetrate into the gland in small septa of fibrous tissue. In older individuals the arterioles are frequently thickened and hyalinized. Thrombosis with calcification and the formation of phleboliths is a common finding in the periprostatic plexus of veins in older individuals. They should not be confused in radiographs with calculi in the prostate or in the urinary system. The exact functional nature of the nerve supply to the prostate in man is not known, but in dogs there are definite secretory nerves, the stimulation of which enhances or decreases the quantity of secretion (14).

Hormonal maintenance of the prostate

THE EFFECT OF CASTRATION. Since the time of John Hunter, it has been known that the removal of the testes results in a prompt and profound atrophy of the male secondary sexual organs, including the prostate. Within the past few decades it has also been shown that the removal of the pituitary will bring about the same atrophy. It follows that these two organs, the testes and the pituitary, secrete some substances which directly or indirectly maintain the epithelium and stroma of the prostate

in a normal state. The injection of testosterone and its esters will restore the atrophic prostate of castration to normal. The injection of the gonadotropic principle of the pituitary in a hypophysectomized animal will give the same effect if the testes are intact. In the reverse direction, the injection of testosterone will depress the activity of the pituitary in the elaboration of the gonadotropic principle. These experimental observations may be briefly summarized as follows: the pituitary gland secretes a hormone which stimulates the testes to secrete another hormone, which in turn stimulates the male secondary sexual characteristics and depresses the activity of the pituitary; thus the pituitary and the testes are in a delicate balance with one another (see chapter on these organs). There is some evidence from human pathology to support this general conclusion. In children and adults with a suprasellar cyst and destruction of the pituitary, there is failure of development or atrophy of the secondary sexual organs. However there are numerous observations that do not fit the simple postulated relations.

During the past decade a variety of hormones have been administered to man for various actual and supposed defects of the hormonal status. It has been repeatedly shown that the injection of testosterone propionate either before or after puberty will bring about hypertrophy and hyperplasia of the prostate. Similarly, the gonadotropic hormones of the pituitary or of pregnancy urine administered to prepuberal boys will induce changes in the prostate, similar to those of puberty. The administration of estrogenic hormones brings about metaplasia in the same structures which show this change at birth (15).

Prostatic secretion

Prostatic secretion in man is an opalescent fluid, which clots and reliquefies within 15 minutes after collection. Median values for components are: 156 m.Eq. sodium, 30 m.Eq. potassium, 30 m.Eq. calcium, 146 m.Eq citrate, 38 m.Eq. chloride, 1 m.Eq. phosphate, 8 m.Eq. bicarbonate, 2.5 grams per cent of protein and 0.286 grams per 100 cc. of lipid, mostly cephalin and cholesterol. Enzymes present include acid phosphatase, β-glucuronidase, aconitase and an enzyme similar to fibrinolysin (Huggins (16)).

Kirk (17) has shown that there is a decrease in the concentration of acid phosphatase in the secretion with increasing age. This is true as well in patients with nodular hyperplasia.

In dogs cholinergic agents promote the volume of secretion.

Morphological changes with increasing age

The prostate gland increases progressively in size from the third to the ninth decade of life, but the slight increase of 2 to 3 cubic centimeters is not statistically significant, if manifestly diseased glands are excluded

from consideration (3, 18). The normal adult prostate measures 2.75 by *3.60 by 1.89 centimeters and weighs 20 to 23 grams. At the end of the* fourth decade and at the beginning of the fifth decade, unmistakable histological changes occur, which are, so far as can be determined, independent of any recognized disease process (3). These changes occur progressively, but they are conveniently grouped into those which occur during a presenile period and those of a senile period. The presenile period extends from the fortieth to the sixtieth year of life. During this time the outstanding characteristic is the variation in the appearance of the same structure in different parts of the same prostate. In the stroma there is atrophy of the smooth muscle fibers and a relative increase in connective tissue. The collagen becomes denser and more homogeneous. The acini remain large, but the papillae are less numerous and the epithelial cells tend more to the cuboidal type. This atrophy occurs irregularly throughout the gland, being advanced in one lobule and inconspicuous or absent in another lobule.

In the prostate taken from an individual over sixty years of age the processes are more static and progress more slowly. The greater part of the organ is involved and there is less variation from lobule to lobule. In focal areas, the acini undergo complete atrophy and are replaced by a mass of loose connective tissue (see figs. 1–4). Within the acini, numerous corpora amylacea are formed, probably as the result of stagnation of secretion and loss of the muscular activity of the organ (3).

In summary the criteria of senile atrophy of the prostate may be listed as follows:

1. Slight irregularities in the character of the epithelium begin between 40 and 45 years.
2. Lobular atrophy begins between 45 and 50 years.
3. The glandular epithelium loses its secretory activity between 50 and 60 years.
4. Complete atrophy of the acini first appears between 60 and 65 years.
5. Atrophy of smooth muscle and increase of the fibrous tissue of the stroma is first apparent between 60 and 70 years.
6. Laminated corpora amylacea increase in size and number after 65 years.

It is possible by an evaluation of these histological features to estimate the age of an individual from a gross and microscopic examination of the prostate (3). In certain persons the age is underestimated and these may be designated as examples of delayed senility. In other instances, the age is overestimated because of pathological involution. *Infections of the prostate* and many chronic debilitating diseases such as cancer and tuberculosis bring about involution and atrophy inconsistent with the age of the individual.



FIGS. 1 TO 4. *Atrophy in the senile prostate*

[illegible]

Physiological changes with increasing age

Whether or not there is an identifiable climacterium in men comparable to that in women is debatable (19). Certainly, as regards subjective symptoms, there is little to support the idea. With objective measurements, there are the morphological changes outlined in the preceding section, and certain easily identifiable physiological changes. Assay of the urinary androgens reveals a decreased excretion of androgen in all men over 40 to 50 years of age (20, 21). There are conflicting reports concerning the urinary estrogens (22, 23). Some investigators find no significant decrease with increasing age, while others report as great a decrease in estrogens as in androgens. Urinary prolan has also been studied and the preponderance of evidence indicates that there is no increase such as is regularly found following the climacterium in women (24).

Sexual drive and libido

In the older man, objective measurements of sexual drive are at the present time difficult or impossible. So far as can be determined there are no morphological changes regularly associated with loss of libido or with impotence. It might be assumed that the atrophy of the prostate and the lack of normal secretion in the older man would severely reduce the reproductive potentialities. The studies of Lange (25) indicate that if a man has previously been married, and is not older than 25 or 30 years when a bilateral orchidectomy is done, about one-half continue a normal libido and potency. In a series of 125 men, castrated under the German law for criminal sex offenses, Rössle (26) states that libido was weakened in approximately one-half of the cases. In the seven men studied by Hammond (27), castration after sexual maturity did not abolish libido. The evidence suggests that in men in whom the psychic and neuromotor behavior patterns of sexual activity have been established, complete loss of the testes does not necessarily prevent participation in sexual activity. It is to be hoped that some investigator will crystallize a research program for the objective measurement of sexual drive in the human being. This program must include not only anatomical and physiological studies, but also psychological measurements, as the mental state of man materially influences sexual drive.

Diseases of the prostate in senility

During childhood and adulthood the prostate is rarely the seat of disease, except in association with gonorrhea. There are rare cases of metastatic abscess in association with infective diseases or pyemia. After the age of 40, for reasons not entirely known at the present time, a variety

of diseases make their appearance. According to many urologists, chronic prostatitis of a non-specific nature, frequently abacterial, is present in from 10 to 35 per cent of all men over the age of 35 (28). Prostatic calculi, either as an incidental finding at autopsy, or as a lesion producing clinical signs and symptoms, are rarely found before the age of 40 or 50 (29). During the sixth decade of life the prostate is frequently slightly to moderately enlarged, soft, and shows on section numerous dilated acini filled with a cloudy white secretion. This type of morphological change is at times associated with slight urinary hesitation and a sense of fullness in the perineum. Of the greatest importance for the health and well-being of the older man is the study of two characteristic diseases: nodular hyperplasia and carcinoma. These two are discussed in separate sections below. Investigations to explain the development of these two diseases in the senile prostate are urgently needed. A number of possibilities immediately come to mind: decrease of sexual activity and consequent inadequate emptying of prostatic secretion, stagnation of secretion from a loss of tone of the smooth muscle of the stroma, decreased hormonal stimulation by androgens and probably by estrogens, atrophy of the epithelium and of the stroma, and circulatory changes from arteriosclerosis and venous thrombosis. The elucidation of these and other factors will require precise and exact investigations on both man and experimental animals.

Nodular Hyperplasia of the Prostate

The disease of the prostate which produces urinary obstruction in elderly men has been known since the earliest days of medicine, and designated by a variety of names, the more prominent of which have been: benign hypertrophy, benign enlargement, adenoma, adenomatous hypertrophy and nodular hyperplasia. Unfortunately the term benign hypertrophy has been the most commonly used. It is both inexact and redundant. The term adenoma is also objectionable since there is no evidence that this disease is a true neoplasm. The most desirable name for a disease of unknown etiology is one based on noncommittal anatomical or histological terms. With these principles, nodular hyperplasia is the most noncommittal of etiology, the most expressive of the anatomical changes, and the most exclusive of closely related clinical and pathological conditions, and could with profit be adopted into medical terminology. The pathological entity should not be confused with the clinical syndrome of prostatism, which means nothing more than that there is obstruction or irritation at the neck of the bladder or in the prostatic urethra, resulting from any of a wide variety of lesions: infection, fibrosis, atrophy, nodular hyperplasia, or carcinoma.

Histogenesis

Careful histological studies of unselected prostates removed at autopsy reveal that the smallest and presumably the earliest lesion is a nodular hyperplasia of the stroma in the wall of the urethra (30, 31). Less commonly there is simultaneous nodular hyperplasia of the stroma and hyperplasia in ducts and adjacents parts of the lateral and middle lobes. The nodules continue to increase in size, apparently by multiplication of the



contained cells, and not by conversion of the surrounding tissue, except in the case of epithelium. As expanding nodules come in contact with ducts or glands these structures are pressed out on the surface of the nodule. *The epithelium on the side toward the nodule undergoes hyperplasia* and evaginations extend down into the nodule (see fig. 5). The epithelium on the side away from the nodule retains the atrophic character of the epithelium of the senile prostate. In microscopic section these encircling glands are the most characteristic feature of the disease and are not found in any other pathological lesion (32). The proliferating stroma about the urethra *is completely lacking in elastic fibrils and can be readily identified* with special stains. The stromal cells are intimately associated with large num-

bers of thick-walled sinusoidal vascular spaces in a way not unlike that which has been described in the small myoma of the uterus. Some of the nodules continue to develop as pure stroma, and never acquire epithelial elements. These are frequently spoken of as leiomyomata of the prostate (33). On the basis of histogenesis they do not differ in any respect from the more usual fibroglandular nodules. In the well developed disease there are numbers of small and large nodules throughout the lateral and middle lobes of the prostate. The epithelium is not unlike that of normal adult prostate, but there is less evidence of secretory activity. The glands for the most part are connected with the ductal system (34). The histogenesis of the nodules in the middle lobe presents a special problem According to the earleir investigations of the French school and of Tandler and Zuckerkandl (35), the nodules of hyperplastic tissue which project into the floor of the trigon are derived from the periurethral accessory glands of Albarran. There is increasing evidence that this is not true, but rather that the nodules are basically derived from the periurethral stroma. It has been suggested that this stroma is a part of the Müllerian duct system, and therefore basically a female structure (31). More careful embryological studies will be needed to confirm this theory.

TABLE 1

Incidence of carcinoma and benign hypertrophy of the prostate

Age group	Prostates examined	Per cent which show carcinoma	Per cent which show benign hypertrophy	Per cent of carcinomas which arose in a prostate with benign hypertrophy	Per cent of benign hypertrophy which also show carcinoma
21–30	24	0%	0%	0%	0%
31–40	28	0%	4% (1)	0%	0%
41–50	23	17% (4)	30% (7)	25%	14%
51–60	65	14% (9)	37% (24)	50%	21%
61–70	77	23% (18)	67% (52)	66%	23%
71–80	63	21% (13)	68% (43)	46%	14%
81–90	24	29% (7)	75% (18)	71%	27%

Incidence

Few authenticated examples of nodular hyperplasia have been reported in individuals less than 40 years of age. The average age when the disease drives the patient to seek medical advice is 63 years. The practicing urologist sees fewer numbers both before and after this age. In sharp contrast to these figures for the clinical disease, is the progressive increase in the incidence in unselected autopsy material, as shown in table 1. Most observations concerning the incidence of benign hypertropy, as with so

many other points which have to do with sex, are based on clinical impressions and semi-medical lore. It has been stated that men who lead celibate lives are either especially subject to, or are spared from, this disorder (36). Earlier statements that the condition is rare in Negroes have not been substantiated by exact observations. Smith and Jaffé (37) found an essentially similar incidence in the white and Negro men coming to autopsy at the Cook County Hospital. Similar conclusions have been arrived at from studies of the material at the Charity Hospital in New Orleans (38–41). If there is any difference it is that the Negro shows clinical symptoms about a decade before the white man. In Chinese, the accurate studies of Chang and Char (40) present evidence that nodular hyperplasia in this race has a markedly lower incidence than in the white and Negro races. As compared with an average incidence of 47.2 per cent in foreigners (Caucasians—largely White Russians), only 6.6 per cent of Chinese over 51 years of age presented histological evidence of benign hypertrophy. The reasons for this difference are not immediately apparent. The religious prohibitions of Buddhism may play a rôle, but this does not seem probable. Contributory evidence on whether or not it is racial would be given by studies of the incidence of benign hypertrophy among the Chinese living in larger American cites, where the environment, and to a certain extent the food supply, would be different from that in Peiping. There is no accurate information on the frequency of the disease among the native tribes of Australia and Africa, but it is said that the condition is rare (41).

Etiological factors

Theories concerning the etiology of nodular hyperplasia have gone through many cycles. Virchow (42) originally postulated that the condition was a true neoplasm, and this thought dominated medical thinking for half a century. With the initiation of extensive histological studies in Germany toward the end of the nineteenth century, two observations led to the development of theories of etiology. Ciechanowski (43) held that long-continued chronic inflammation results in the diffuse and nodular hypertrophy of the gland. But, in accordance with the teaching of Virchow, he acknowledged that true adenomas and myomas occur. The French school, led by Launois (44), were impressed with the finding of arteriosclerosis of the vessels of the external circulation, and postulated that the hyperplasia of the internal part of the prostate was an attempt to compensate for the atrophy of the external part. White (45), in the United States, developed the idea that if castration resulted in atrophy of the normal prostate, it should be valuable in the treatment of the enlarged prostate. Endocrinology was not at that time sufficiently advanced to take advantage of this suggestion. The clinicians of the time were too

biased and prejudiced to evaluate the findings scientifically. With the isolation and synthesis of the sex hormones in the early 1930's, the cause of a disease in a secondary sexual organ was naturally referred to some disturbance of these hormones.

However, there is no agreement on the exact mechanism. Huggins has postulated that the long continued action of androgen on the part of the prostate with a low threshold is the causative factor. Others have suggested that the changing ratio of androgens to estrogens is an important factor. The observation of a relative excess of aetiocholanolone over androsterone by Robinson and Goulden (46) may be significant.

Treatment

Nodular hyperplasia has been treated by four groups of procedures: surgical removal of the hyperplastic tissue, ligation of the vas deferens according to the technique of Steinach, irradiation, and alteration of the hormonal status. The scientific position of prostatectomy, suprapubic, perineal, or transurethral, needs no discussion. It remains as the only completely satisfactory and proven method for the treatment of the condition. The operation of Steinach has both proponents (Elliot-Smith (47) and opponents (Jacobs (48)); and in the opinion of the reviewer is of no value, since it is based upon a fundamentally faulty concept—that ligation of the vas deferens in a sexually mature individual brings about a morphological and functional hyperplasia of the interstitial cells of the testes. Irradiation by x-ray probably decreases the associated infection and edema, but has little effect on the hyperplastic tissues (49). Alteration of the hormonal status of the individual may involve either depriving him of his own testicular hormones by castration, or the injection of an additional source of some hormone. The operation of castration, as proposed by White (45), was abandoned in the early twentieth century, largely because of the introduction of the operations of prostatectomy. It has recently been revived by Huggins and Stevens (50). Histological studies indicate that the hyperplastic tissue undergoes atrophy, and it is possible that further developments in this field may give satisfactory results. Certainly it should be attempted with those patients who refuse the usual operative procedure, or who are too ill for it. Precise clinical and morphological investigations should be employed to study this subject. The administration of hormones has in general given variable results, regardless of the identity of the hormone (reviews by Vidgoff (51); and Lower, Schlumberger, and Ferguson (52))—androgen (Keller and Hull (53); Heckel (54), estrogen (Hamilton, Heslin, and Gilbert (55), or inhibin (McComb and Pearse (56)); and Lower (57)). Improvement has been repeatedly reported but the studies of Clarke (58) clearly show that temporary periods of improvement are to be ex-

which the primitive ovocytes failed to migrate into the genital ridge. The absence of germ cells is always associated with a complete failure of the formation of follicles and therefore complete lack of ovarian estrogens.

On the other hand a comparable condition which occurs in the male is described by del Castillo, Trabucco and de la Balze (5), and others and designated by Engle (6), as *germinal aplasia*. In these cases no germ cells are present, no sperm ever develops but interstitial cells may be abundant, and the testicular androgen production may be no different than normal males. Thus it is seen that hormone production in woman is dependent on the presence of ova, but in the man androgen production may be completely independent of sperm production.

In the preceding paragraph circumstances which occur in the human male and female have been described. There is a school of thought, which was led by E. Allen, which believes that in some laboratory animals, e.g., rat and mouse, a post-natal development of new ova occurs. With reference to the ageing process, it is known that in many animals the ovary is full of ova at old age and that in many females of various species, rat, cat, goats mares, reproduction can and does occur at advanced ages for the species, (6). It appears that only the human female ceases reproduction at an age much younger than the expected chronological life span.

Endocrine Integration

The development of the genital system and the attainment and maintenance of functional adequacy are to a certain degree interrelated with endocrine factors.

The testis is composed of two types of tissue. The seminiferous tubules contain the cells which produce and nourish the developing spermatozoa. In the intertubular spaces are found the blood vessels, lymphatics, loose connective tissue and the specialized interstitial cells, or cells of Leydig. These latter cells are generally accepted as the cells of origin of one or more of the male sex hormones.

Two groups of hormones are involved in the maintenance of the reproductive system. One group consists of those which act only on the gonad, cause it to function properly and are known as gonadotropins. These are the gonad stimulating hormones of the anterior pituitary gland. Two other well known gonadotropic hormones occur in the human. One of these is found in the blood and urine of pregnant women and in the human placenta. The other, qualitatively different, is found in the blood or urine of women after the menopause or ovariectomy and in men after castration.

The second group of hormones are the sex hormones which in nature are

produced by the gonads in response to the action of gonadotropic hormones on the ovary or the testis. Certain female sex hormones discussed in the previous chapter are known collectively as estrogens and the male sex hormones as androgens.

Maintenance of genital function in the male depends on the proper balance of gonadotropins, estrogens and androgens.

One gonadotropic factor, frequently referred to as the "luteinizer" because of its action on the ovary, exerts its action on the interstitial cells, causing the production of androgens. Androgens thus produced act on all the other genital organs and probably with other endocrines, on the entire body. Certain experimental evidence indicates that the estrogens also have a role in the male genital system, although it is not clear what effects estrogens may cause in the man, nor in what organ they may be produced. As will be shown below, substances identified as estrogens as well as androgens are found in the urine of normal men.

One gonadotropin also acts directly on the seminiferous epithelium, maintaining sperm production and, at least in the rat, certain androgens will maintain sperm production. The experimental evidence on rats indicates that one gonadotropin, (which again because of its action in the female is called a follicle stimulating hormone), acts on the seminiferous tubule, although its effect is enhanced if it is given with the interstitial cell stimulator (the luteinizing factor). Either by this means, or experimentally by direct administration of an androgen, the spermatogenic function is maintained.

It is known that the human male by the fifth fetal month shows an enormous hyperplasia of the interstitial cells, which is maintained until after birth. This hyperplasia undergoes involution after birth, in the same manner as the fetal uterus. The seminiferous tubules, however, do not change appreciably during this period. Experiments with appropriate gonadotropic hormones in rats and monkeys indicate that the quantitative increase of the interstitial cell mass caused by the injection of gonadotropic hormone of human pregnancy is greatest in early life. Thus, a marked interstitial cell hyperplasia can be caused in young animals. It is thought by some that this same hormone which is present in the blood of pregnant women is responsible for the natal hyperplasia as well as for the prenatal descent of the testis. However, this tissue loses its capacity to respond to this gonadotropic hormone by hypertrophy. The interstitial cells of a normal adult rat or monkey may be induced to produce androgens as shown by the growth of accessory organs but will not show marked hyperplasia.

The interstitial cells of the testis will respond, from or before birth, to

many other points which have to do with sex, are based on clinical impressions and semi-medical lore. It has been stated that men who lead celibate lives are either especially subject to, or are spared from, this disorder (36). Earlier statements that the condition is rare in Negroes have not been substantiated by exact observations. Smith and Jaffé (37) found an essentially similar incidence in the white and Negro men coming to autopsy at the Cook County Hospital. Similar conclusions have been arrived at from studies of the material at the Charity Hospital in New Orleans (38–41). If there is any difference it is that the Negro shows clinical symptoms about a decade before the white man. In Chinese, the accurate studies of Chang and Char (40) present evidence that nodular hyperplasia *in this race has a markedly lower incidence than in the white and Negro* races. As compared with an average incidence of 47.2 per cent in foreigners (Caucasians—largely White Russians), only 6.6 per cent of Chinese over 51 years of age presented histological evidence of benign hypertrophy. The reasons for this difference are not immediately apparent. The religious prohibitions of Buddhism may play a rôle, but this does not seem probable. Contributory evidence on whether or not it is racial would be given by studies of the incidence of benign hypertrophy among the Chinese living in larger American cites, where the environment, and to a certain extent the food supply, would be different from that in Peiping. There is no accurate information on the frequency of the disease among the native tribes of Australia and Africa, but it is said that the condition is rare (41).

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pected in this condition, and that in the one series of 93 patients studied by him, individuals who refused operation got along at least as well as those who were operated upon for an average period of four years.

Clinicopathological correlation

The obstruction of the prostatic urethra and the presence of a pool of residual urine in the bladder are the most obvious clinical consequences of the pathological enlargement of the prostate. However, there is no evidence that the size of the prostate is related to the degree of urinary obstruction. The urethra in benign hypertrophy is markedly enlarged and it is more than probable that a physiological disturbance of the muscle at the neck of the bladder plays an important role in the obstruction. In view of the introduction of the hormonal treatment during the past few years, some method for the accurate estimation of the size of the prostate without instrumentation of the urethra and without massage of the enlarged gland is urgently needed. Progress has already been made by Peirson and Wilson (59) in the development of a radiographic method.

Prostatic hypertrophy in dogs

Most dogs over 8 or 10 years of age have an enlarged prostate, which, in some instances, causes urinary obstruction. Histological studies show that the enlargement is usually caused by a diffuse hyperplasia of the entire gland, but a few examples of nodular hyperplasia have been reproted. A few dogs, on the contrary, show a progressive atrophy of the prostate after the sixth year of life. In a group of 243 dogs studied by Zuckermann and McKeown (60), it was reported that "isolated adenomatous nodules such as are seen in the human prostate, of the sort that can be 'shelled out', were not seen in any of our specimens." Zuckermann and Groome (61) observed metaplasia in one enlarged canine prostate similar to that which is produced by the injection of estrogens, and which is seen in the human prostate in association with senility and benign hypertrophy. It is possible that the condition in man and in the dog are slightly different expressions of the same hormonal disturbance. Further studies are desirable.

The posterior lobe in benign hypertrophy

As noted above the true posterior lobe of the prostate does not participate in the nodular hyperplasia of benign hypertrophy. It is compressed and stretched over the surface of the enlarged gland, and is called the surgical capsule of the prostate by many urologists. The microscopic examination reveals atrophy of the epithelium and stroma independent of the degree of compression, indicating that as certain structures of the

lateral and middle lobes undergo hyperplasia the posterior lobe is uninfluenced and undergoes the usual type of senile atrophy. Any theory of the etiology of benign hypertrophy must take this observation into consideration. It also serves as support for the idea that benign hypertrophy is in some way related to the female phase of sex, since the posterior lobe is a distinctly male structure, while the lateral and middle lobes are ambisexual structures.

Experimental production of benign hypertrophy

It may be categorically stated that nodular hyperplasia in an experimental animal has not been produced. In one rat, Jenkins, Deming and Von Wagenen (62) have observed a focus of stromal hyperplasia not unlike that of man, indicating that this animal may be a suitable one for experimental work.

Carcinoma of the Prostate

Carcinoma of the prostate is distinctly a disease of the later decades of life. In the series of 1326 examples of carcinoma of the prostate collected by Joeck (63), only 7 occurred in patients under 40 years of age. In the same series the prostate ranked sixth in the order of frequency of 22,139 cancers. Stomach, bronchus, colon, esophagus, and the remainder of the intestine preceded it in that order. Among 125,740 deaths from cancer among the industrial policy-holders of the Metropolitan Life Insurance Company, 1,904 were reported as caused by carcinoma of the prostate (Duff (64). Fifteen of these were in individuals less than 35 years of age, and the death rate from this condition progressively increased to a figure of 67.1 per hundred thousand over the age of 75.

There is some evidence that carcinoma of the prostate has increased in frequency, although this conclusion must be qualified by a consideration of many contributing factors. According to the compilations of Hoffman (65), the rate for carcinoma of the prostate per hundred thousand men has increased from 3.6 to 8 in the period from 1920 to 1931. During an almost similar period the figures for England and Wales rose from 4.18 to 7.53. These figures are of course based on clinical diagnoses. Heimann (66), in a study of the records of the Prussian State Hospitals for the years 1895 and 1896, found among 2929 instances of carcinoma only 17 examples of carcinoma of the prostate—a remarkably low figure as compared with the incidence of the disease in routine autopsies today. This is in sharp contrast with the other common carcinomas, such as those of the stomach and colon, which showed about the same incidence as in 1940.

In Europe and America there are only slight differences in the incidence of carcinoma of the prostate. On the other hand, in the Chinese,

carcinoma of the prostate is a rare disease. In the collected series of Hu and Ch'in (67) there was only one carcinoma of the prostate in 379 carcinomas in men and in a total of 821 carcinomas coming to autopsy in the Hospital of the Peiping Union Medical College. The most common carcinoma in Chinese men is of the penis. Tumors of this organ constitute 25 per cent of all carcinomas in men. In women carcinoma of the cervix ranks first and comprehends 60 per cent of all malignant tumors in the female sex.

Latent carcinoma of the prostate

All of the above statistics are based upon the presence of a clinically manifest carcinoma of the prostate. Of equal importance to the investigator and the student of oncology is what might be termed the latent carcinoma of the prostate. Routine histiological examination of the prostate at autopsy by Rich (68) at Johns Hopkins Hospital showed a carcinoma in 14 per cent. Systematic investigation of a series of 252 unselected prostates of men over 41 years of age by the step section method revealed carcinoma of the prostate in 21 per cent (Moore (69). The frequency progressively increased from 17 per cent in the fifth decade to 29 per cent in the ninth decade (see table 1). Similar but slightly lower figures were secured by Muir (70), in a study of only 54 unselected prostates. Although there can be no doubt concerning the histological character of these neoplasms, their significance is not apparent. It seems probable that they represent small carcinomas which, if the patient had lived, would have developed into clinically manifest tumors. There is also the inference that carcinoma of the prostate develops slowly over a long period of years.

Occult carcinoma

The latent carcinoma should be distinguished from the occult carcinoma (Culp (71)). By this latter term is meant a carcinoma with widespread metastases from a small, unsuspected, primary growth. Occult carcinoma of the prostate is not uncommon, and the first clinical evidence of the disease may be a compression fracture of one of the vertebral bodies. Palpation of the prostate through the rectum should be a part of the physical examination of every older man.

Histogenesis

Since carcinoma of the prostate is so distinctly a disease of elderly men, it follows that the etiology and histogenesis of the condition probably depend on some previous alteration incident to the ageing process. Histological examination confirms this impression (Moore (69)). Latent carcinomas are found only in atrophic glands, and it appears that the malig-

nant cells are directly derived from atrophic cells. The great majority of tumors are derived from tissues of the posterior lobe. The actual figures vary from 40 to 75 per cent, depending on the investigator.

Relation to benign hypertrophy

In early investigations of Albarran and Halle (72) it was postulated that 14 per cent of all examples of benign hypertrophy also showed some areas of carcinoma. This teaching was accepted by the majority of urologists and pathologists. During the last decade more exact investigations have thrown considerable doubt on this conclusion (73, 74). In the large number of individuals who have been operated upon for benign hypertrophy at the James Buchanan Brady Urological Institute by Dr. Young and his associates, there are only two instances in which a carcinoma arose in a pre-existing area of benign hypertrophy (75). In the series of 53 latent carcinomas studied by Moore (69), 2 arose in an area of benign hypertrophy, or an incidence of 4 per cent.

Pathology

Carcinoma of the prostate appears within the gland as a firm, white, indefinitely outlined mass, usually in the posterior lobe. Within the white fibrillar tissue small yellow flecks, representing the neoplastic epithelium, can usually be identified. The tumor cells invade the lymphatics early, and grow into the capsule and into the seminal vesicles (69). Metastases are found first in the lymph nodes about the internal iliac artery, and then in the nodes about the aorta Direct extension from these latter lymph nodes into the vertebral column may be the explanation for the frequent involvement of this structure (70). In late cases there are metastases to the lungs and liver. Microscopically most of the tumors are adenocarcinomas, but carcinoma simplex and small cell carcinoma occur.

Examination of the prostatic secretion for cancer cells by the technique of Papanicolaou holds promise of earlier and more exact diagnosis (Herbut and Lubin (71),.

Treatment

In the early stage the treatment of choice is a radical perineal prostatectomy. In the experience of Young (72) a cure should be attained in 50 per cent of favorable cases.

In the more advanced stage some form of antiandrogenic therapy should be employed.
experience of
relapse, and 7 ,
may live for extended periods of eight to ten years.

Orchiectomy may result in hot flashes which are abolished by administration of estrogens. Long continued use of estrogens causes testicular atrophy and mammary hypertrophy. Rarely bilateral carcinoma of the breast occurs (74)

The carcinoma cells under the influence of estrogens undergo hydropic and fatty degeneration with pyknosis of the nuclei (75). In the remaining prostate there is atrophy, more marked in the anterior parts, and metaplasia near the urethra (76).

Experimental carcinoma

By injection of carcinogenic chemicals Moore and Melchionna (77) produced squamous cell carcinoma and sarcoma of the prostate of the rat. Horning (78) reports the production of adenocarcinoma in autogenous transplants of the mouse prostate exposed directly to crystals of 20-methylcholanthrene.

Deming and Hovenanian (79) have transplanted human carcinoma of the prostate to the eyes of guinea pigs.

Clinicopathological correlation

Unfortunately most carcinomas of the prostate arise and continue to grow for months or years in the posterior lobe, a clinically silent area. It is only when the tumor invades the urethra or the neck of the bladder to produce urinary obstruction, or surrounds the rectum with resulting constipation or difficulty in defecation, that the patient becomes aware of the disease. When either of these structures has become involved, radical surgical removal is probably not feasible. The correct diagnosis of occult carcinoma of the prostate has been greatly facilitated by studies on the acid phosphatase of the blood plasma. An elevation of the serum acid phosphatase in the presence of bony metastases is found regularly with carcinoma of the prostate and rarely with any other tumor (80).

SUMMARY

Accurate information concerning changes in the male secondary sexual organs with increasing age is lacking, except in the case of the prostate.

In the prostate there are definite and specific histological changes after the age of 40 which occur in most men and which are directly correlated with the ageing process. Physiological studies, especially of the urinary excretion of steroid hormones, have not given consistent results. Physiological and anatomical methods for the study of the hormonal status of men, similar to the vaginal smear method for women, are needed.

The problem of the relation of male impotence to age is so complex, and the sexual life of older men is so complicated by changes, both in the inner

physiological environment, and in the external social surroundings, that little can be said at the present time.

Nodular hyperplasia of the prostate is a common disease after the age of 40 years. Histological studies indicate that the primary site of proliferation is in the periurethral stroma, and that glands and epithelium are only secondarily involved. The best working hypothesis of the etiology of this condition is that it is a disturbance in the ratio and the total quantity of effective androgen and estrogen. The treatment of the condition with hormones should be continued on an experimental basis, but precise clinical and pathological observations should be made of these patients

Carcinoma of the prostate is far more common than is generally recognized, and the examination of prostate should be a routine part of the physical examination of every older man. In general, all methods of cure have failed except the radical operation of Young. This procedure should be more widely used.

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27

THE MALE REPRODUCTIVE SYSTEM

EARL T. ENGLE

New York

Involution of the reproductive organs of woman and of man as a part of the ageing process present marked and striking differences.

The ovary of woman has a full complement of ova at birth. It is probable that at birth all the eggs are present that will ever be formed. Ova are being destroyed at birth and are not replaced. Thus the 200,000 or 400,000 ova which are present are not replenished, and in this sense ageing begins at birth. One of the characteristics of the ovary is the continuing loss and destruction of ova as a normal process, until at the menopause all of the ova are gone (1, 2, 3).

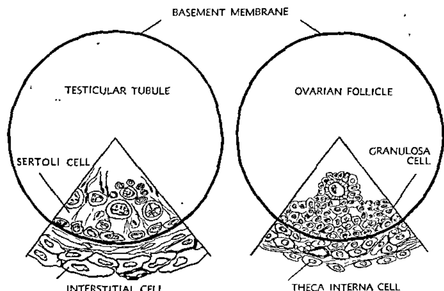
Also marked changes occur in the ovarian arteries with fibrosis and hyalinization being commonly observed in middle and older age groups.

In woman the endocrine function of the ovary is directly dependent on the presence of the ovum and the growth and differentiation of the follicle and the theca interna which is the site of production of the estrogens. If no ova are present there will be no growing follicles and hence no estrogen production. Thus the reproductive life and the endocrine components for regulation of the genital system cease abruptly around 45 to 50 years of age.

The process of involution in man is quite different. In the first place hormone production is not dependent on the presence of the germ cells. A man is born with a testis which is separated into two functional units, one, the interstitial cells, for the production of steroid hormones, the androgens; the other, the seminiferous tubules for the production of germ cells.

In the sperm-producing tubules are present at birth the undifferentiated cells which give rise to the sustentacular cells of Sertoli, and others to the primary germ cells. The spermatogonia divide throughout life, giving rise

to countless number of other germ cells, and through successive generations of specialized cells, to the spermatozoa. Thus while a woman, during her 30 years of reproductive life will liberate fewer than 400 ova capable of



b. The supply of ova is definitely limited, and all ovarian ova are gone by the

woman and of man.
From Engle, 1951, Problems of Aging, Proc. 13th Conference, Josiah Macy Jr. Foundation.

being fertilized, man will manufacture spermatozoa in truly astronomical numbers.

The contrast between the interrelation of germ cells and hormone pro-
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which the primitive ovocytes failed to migrate into the genital ridge. The absence of germ cells is always associated with a complete failure of the formation of follicles and therefore complete lack of ovarian estrogens.

On the other hand a comparable condition which occurs in the male is described by del Castillo, Trabucco and de la Balze (5), and others and designated by Engle (6), as *germinal aplasia*. In these cases no germ cells are present, no sperm ever develops but interstitial cells may be abundant, and the testicular androgen production may be no different than normal males. *Thus it is seen that hormone production in woman is dependent* on the presence of ova, but in the man androgen production may be completely independent of sperm production.

In the preceding paragraph circumstances which occur in the human male and female have been described. There is a school of thought, which was led by E. Allen, which believes that in some laboratory animals, e.g., rat and mouse, a post-natal development of new ova occurs. With reference to the ageing process, it is known that in many animals the ovary is full of ova at old age and that in many females of various species, rat, cat, goats mares, reproduction can and does occur at advanced ages for the species, (6). It appears that only the human female ceases reproduction at an age much younger than the expected chronological life span.

Endocrine Integration

The development of the genital system and the attainment and maintenance of functional adequacy are to a certain degree interrelated with endocrine factors.

The testis is composed of two types of tissue. The seminiferous tubules contain the cells which produce and nourish the developing spermatozoa. In the intertubular spaces are found the blood vessels, lymphatics, loose connective tissue and the specialized interstitial cells, or cells of Leydig. These latter cells are generally accepted as the cells of origin of one or more of the male sex hormones.

Two groups of hormones are involved in the maintenance of the reproductive system. One group consists of those which act only on the gonad, cause it to function properly and are known as gonadotropins. These are the gonad stimulating hormones of the anterior pituitary gland. Two other well known gonadotropic hormones occur in the human. One of these is found in the blood and urine of pregnant women and in the human placenta. The other, qualitatively different, is found in the blood or urine of women after the menopause or ovariectomy and in men after castration.

The second group of hormones are the sex hormones which in nature are

produced by the gonads in response to the action of gonadotropic hormones on the ovary or the testis. Certain female sex hormones discussed in the previous chapter are known collectively as estrogens and the male sex hormones as androgens.

Maintenance of genital function in the male depends on the proper balance of gonadotropins, estrogens and androgens.

One gonadotropic factor, frequently referred to as the "luteinizer" because of its action on the ovary, exerts its action on the interstitial cells, causing the production of androgens. Androgens thus produced act on all the other genital organs and probably with other endocrines, on the entire body. Certain experimental evidence indicates that the estrogens also have a role in the male genital system, although it is not clear what effects estrogens may cause in the man, nor in what organ they may be produced. As will be shown below, substances identified as estrogens as well as androgens are found in the urine of normal men.

One gonadotropin also acts directly on the seminiferous epithelium, maintaining sperm production and, at least in the rat, certain androgens will maintain sperm production. The experimental evidence on rats indicates that one gonadotropin, (which again because of its action in the female is called a follicle stimulating hormone), acts on the seminiferous tubule, although its effect is enhanced if it is given with the interstitial cell stimulator (the luteinizing factor). Either by this means, or experimentally by direct administration of an androgen, the spermatogenic function is maintained.

It is known that the human male by the fifth fetal month shows an enormous hyperplasia of the interstitial cells, which is maintained until after birth. This hyperplasia undergoes involution after birth, in the same manner as the fetal uterus. The seminiferous tubules, however, do not change appreciably during this period. Experiments with appropriate gonadotropic hormones in rats and monkeys indicate that the quantitative increase of the interstitial cell mass caused by the injection of gonadotropic hormone of human pregnancy is greatest in early life. Thus, a marked interstitial cell hyperplasia can be caused in young animals. It is thought by some that this same hormone which is present in the blood of pregnant women is responsible for the natal hyperplasia as well as for the prenatal descent of the testis. However, this tissue loses its capacity to respond to this gonadotropic hormone by hypertrophy. The interstitial cells of a normal adult rat or monkey may be induced to produce androgens as shown by the growth of accessory organs but will not show marked hyperplasia.

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The present data, while not conclusive, indicate that a period of cellular differentiation and ripening of the tubule is necessary before sperm production can be induced. There is agreement that sperm production in animals cannot be precociously induced by any androgen or gonadotropin (7, 8, 9, 10). Until the tubule has undergone the necessary development independent of these particular hormones it cannot respond to an otherwise adequate gonad activator. In the human female at least the same loss of reactivity of the ovary is seen at the menopause. It is not known whether or when a similar loss of reactivity is shown by the testis, but in the light of all other data it is to be anticipated.

Both androgens and estrogens are excreted in the urine by both men and women. Small amounts of each have been found in children, both boys and girls. Kochakian (11) found that young men between 21 and 29 excreted 12 to 16 capon units per liter, while 5 men, 50 to 72 years of age, excreted an average of 2 to 3 capon units.

Koch (12) gives as a normal range of androgens in mature men 40 to 100 I.U. of androgen, and of normal women 30 to 100 I.U. of androgen (see also 13, 14, for further studies).

One of the characteristics of the menopause is the increase in excretion of gonadotropic substance, which is concomitant with decrease or cessation of ovarian function. That the relationship is a direct one was shown by Albright who inhibited the excretion of gonadotropins by injections of estrone in women. Such a marked increase in production may not be generally true for men. If it does occur in some, its appearance is not so sharply limited to a single decade of life as in women.

The earlier work cited above was done by bioassay methods, while the more recent work has evaluated the excretion of the ketosteroids. Most routine studies using these methods have assayed the 17-ketosteroids. These steroids are excreted in fairly constant amounts by normal individuals and represent the excretion production of substances elaborated by both the adrenal cortex and the testis in the ratio of about 5:3.

Hamilton and Hamilton (15) have reported the excretion of ketosteroids in a unique study. They examined 51 apparently normal men whose ages ranged from 21 to 75 years, in whom no medical disabilities were found. These men were kept under rigidly controlled conditions, with no other selection that that they all have been committed to prison by the court. These investigators have shown that the average daily excretion of ketosteroids decreased progressively, in an almost straight line regression from

the third to the eighth decade of life (fig. 2). It will be noted that this steady decline of this steroid complex does not indicate a sharp break at any age group and indicates no endocrine crisis such as occurs in women in the fifth decade.

Another less elaborate study by Konigsberg, Pearson and McGavack

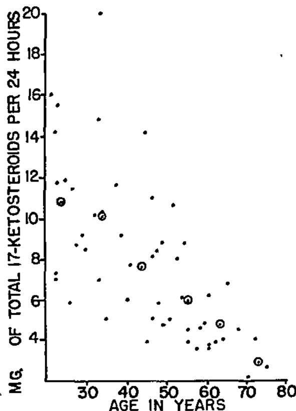


FIG. 2 Excretion of 17-ketosteroids by decades of life. From Hamilton & Hamilton (15).

(16) included studies of 85 males, ranging from 13 to 75 years of age, who for the most part were patients with non-endocrine complaints. Using their own modification of a method for evaluating 17-ketosteroids these workers report an increase in the amount of urinary excretion up to the 35 year age group and a steady decline thereafter.

While the reproductive capacity of the woman is in abeyance from the latter part of the fifth decade, the sexual capacity need not be lost. Sexual function in either sex may be seriously restricted in the presence of adequate

the appropriate gonadotropin, but the seminiferous tubules do not show a similar responsiveness at this age. Neither the ovarian follicle nor the testis tubules will respond to the gonadotropins until a much later age.

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The recent monograph by Turner (22) is an excellent review of the clinical uses of testosterone.

It is not clear whether the role of testosterone in water balance is a normal physiological activity, or a temporary or induced one, as the steroid hormones of the adrenal cortex and the estrogens have similar capacities

The Testis

In the section dealing with ageing in women, it has been made clear that the reproductive function of the woman ceases within a specific age period, although participation in sexual activities need not be severely affected thereby. In men, however, it is probable that sexual activity decreases or is in abeyance before reproductive potentiality is lost, but adequate facts about the relation of testis structure to sexual capacity are not available. Even in domestic animals sexual activity is not synonymous with fertility. It is generally assumed that the interstitial cells of Leydig secrete one or more of the androgens. The facts are better organized when the seminiferous tubules are considered. If no spermatozoa are present, fertility is lost. If spermatozoa are present in the tubules or the epididymis, fertility may be assumed. The recent studies on sperm morphology in relation to male sterility indicate that even an abundance of motile sperm in the ejaculate is no proof of fertility. The percentage of abnormal forms, the short life of the sperm, poor motility, and other factors, may seriously impair the fertility of the man.

In studies of the morphology of the testis in various life decades, the presence of sperm forming cells and the spermatozoa in the tubules and sperm cells in the epididymis merely indicate that this capacity is present at this age and that it is an indication of normal endocrine balance. Within these limitations in interpreting the findings resulting from histological study of the human testis, a few actual observations may be reported.

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hormones, or may continue after the removal of the gonads and restriction of sex hormone production. Those who desire extensive popular discussion of this theme will refer to the well known Kinsey Report.

Metabolic relations of the hormones of the testis

One of the hormones of the testis is prepared as an ester of the chemically pure testosterone and is used therapeutically as testosterone propionate. In such cases this hormone maintains the normal functions of the genital organs and permits participation in normal sexual activity in the absence of the testes.

In addition to its function of maintaining sexual activity and reproductive capacity, all of the steroid hormones, including those derived from the ovary, the testis and the adrenal cortex, perform certain functions in bodily economy which deserve attention. Thus, while the steroid hormones of the ovary and testis are necessary for reproduction they also have other general metabolic effects.

It has been known that creatine-creatinine excretion bore some relation to the metabolism of voluntary muscle. Both boys and girls excrete creatine before puberty. Women may excrete it intermittently, but normal men do not spontaneously excrete creatine. Kenyon and Koch et al. have shown that castrated men excrete creatinine, but this may be reduced or abolished by testosterone therapy.

Jailer (17) has used monkeys for a study of this metabolic relationship and demonstrated that the control of creatine excretion in immature male or female animals is a function of testosterone. Sutton (18), however, has shown that elderly patients with benign prostatic hypertrophy do not differ from other men of the same age group, or from younger men, in their capacity to retain creatine.

Another indication that the androgens affect voluntary muscle, directly or indirectly, has been presented by Hesser, Langworthy and Vest (19), who showed improvement in work performance in cases of myotonia atrophica when the patients were given androgen therapy.

Another important role of androgen in the body is shown by the careful work of Kenyon (20) that testosterone propionate causes a retention of potassium, phosphorus and chlorides in the body and an increase in nitrogen. The reduction in the amount of excreted urea nitrogen corresponds to the retention of several hundred grams of protein. An increase in body weight occurs which is not due entirely to an increased retention of water. After cessation of androgen treatment the stored water is quickly lost, but the weight increment is retained. The assumption is therefore made that new protein has been built into the body structure by the androgen.

Several contributions dealing with experimental animals have shown

that androgens have a renotropic effect, the kidney being increased in size after treatment. In man, Lattimer (21) has shown that the normal kidney does not respond to the administration of androgen, but that hypertrophy of the remaining kidney after unilateral nephrectomy is accelerated by testosterone administration.

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The material falls into two general classes. One group of investigators has reported the microscopical condition of the testis obtained at routine autopsy, in relation to age or to specific conditions of disease. The other group of investigators has studied the testes obtained mainly from surgical castration of psychopathic groups and compared them with testes from individuals dying from traumatic causes. Notable among these studies are those of Sand and Okkels (23, 24, 25). The impressions of the writer are obtained from more than 200 cases where the entire genital tract has

Fig 3

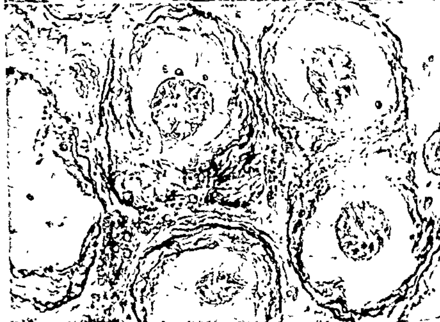


Fig. 4

been available for study, the great majority of them from traumatic deaths with adequate histological fixation.

During the past decade, the use of the technique of the testis biopsy has made available a great quantity of human material. Although the clinical usefulness of this method is applied mostly to the younger age groups, our knowledge of the morphology of the human testis has greatly increased.

The testis tubule

One of the functions of the testis is the production of spermatozoa. Normally spermatozoa are produced beginning during puberty The testes of mature men which have no spermatogenic cells are seen only rarely, the only cells of the tubule being the sustentacular cells of Sertoli (figs. 3 and 4).

The critical problem for the present report is the time at which spermatogenic function fails or ceases and if it is related to the problem of ageing The number of cases is few indeed. Studies of ejaculates are rare Exner (quoted by Blum (26)) reported that in 165 cases of men past 60, spermatozoa were present in 68 5 per cent of men aged 60 to 79, 59 5 per cent at 70 to 80, and 48 per cent at 80 to 90. In our own series more than half of the testes and ducts of men past 70 have abundant spermatozoa

One type of morphological change which occurs with failing spermatogenic action, and may influence it, is in the basement membrane and the capsule of the tubule (tunica propria) Normally this is a delicate basement membrane which is surrounded by laminated collagenous and argyrophile fibers. In all tubules of man or monkey during the ages of sperm formation, this is a thin and delicate membrane if the tubules are in normal spermatogenic condition. The connective tissue of the tunica propria increases in thickness in many individuals, usually with decrease in the size of the tubule.

In its terminal form this is known as fibrosis testis An examination of

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Fig. 3 (Upper) and Fig. 4 (Lower)

Fig 3. Photomicrograph of section of right testis of 45 year old man, death by coronary disease (No 65)

There were a few tubules with apparently normal spermatogenesis but no spermatozoa were present in the epididymis. A few tubules were completely fibrosed, but the majority of tubules in each testis were as represented in the figure. Normal appearing interstitial cells, but the tubules were lined only with Sertoli cells, the spermatogenic cells being absent.

Fig. 4 Photomicrograph of right testis of a 77 year old man, after operation for prostatic hypertrophy (No. 138)

The elastic fibrils at the periphery of the tubules and the greatly thickened collagenous fibers of the tunica propria are characteristic of this fibrosing process The lumen of the tubule is greatly reduced in size, and the Sertoli cells are few in number

many specimens in all decades of life indicates that the replacement of the seminiferous elements of the tubule by connective tissue is a progressive sclerosing process.

The first change in the tubule is a thickening of the basement membrane and of the tunica propria The elastic tissue in the tunica propria does not seem to increase in the early stages and the entire change is in the collagenous fibers. The difference between the testis with a few tubules with thickened basement membrane and tunica propria and complete fibrosis testis is one of degree. It is an impression that the change from the tubule with the thickened tunica to the completely fibrosed tubule is a progressive change and that the ultimate fate of any tubule with the thickened wall would be complete fibrotic obliteration.

The elastic tissue of the tunica propria of the normal tubule consists of delicate fibers dispersed among the collagenous fibers. In appropriately stained material these fibers appear similar to straight slender lines in an etching As the tunica propria increases in collagenous content during the early stages of fibrosis the elastica does not increase in a similar manner By the time that the degenerative sclerosing process has proceeded to the stage where the epithelial structures are severly damaged, the elastic fibers have changed greatly in form. They are found outside of the fibrous layers Instead of an increase in number of the straight, taut, clearly etched lines of elastic fibers, the whole mass has taken on a "woolly" appearance, with much loss of identity of individual fibers. This mesh work of fibers, like skeins of wool, is circularly disposed in the outer portion of the sclerosed tubules, and is not seen in the inner portion of the tubular scar.

Stieve (27) and Spangaro (28) both discuss progressive increase in the elastica content of the tubule wall. Stieve regards the thickening of the wall to be an age change in which the collagenous elements are sacrificed to the elastic fibers. The same changes, according to Stieve, occur in the tunica albuginea and epididymis.

The cellular content of the collagenous portion is greatly reduced, but relatively abundant in the elastica. On histological grounds it would be suspected that this change in structural characteristics of the elastic tissue was evidence of a loss of actual elasticity. There is naturally no available history of previous infection of inflammatory process in the cases studied On histological grounds there is no indication of previous infarction. Of the testes from 58 patients which showed any areas of fibrosis, or with generalized thickening of the tunica propria, spermatogenesis appeared relatively normal in 32 cases, normal in only a few tubules of 7 cases and was absent in 19 cases.

The relation of these degenerative changes to age is clear. It may occur as early as the third decade of life, but about one-third of the cases in the

fifth, sixth and seventh decades showed some increase in fibrous tissue around the tubule, and 5 of 6 cases in the eighth decade were involved. There are no data which indicate an association of this pathological change with other known medical disorders.

In many cases with well advanced fibrosis the interstitial cells appear morphologically normal. In other cases they may appear to be sparse (vide infra).

An interesting feature of the testis of the aged, which probably should be referred to as involutional, was noticed by Simmonds (29) In many testes with thickened basement membrane, he noted that the spermatogenic cells changed into small round cells resembling those of the undeveloped testis.

The effects of hypophysectomy in adult male monkeys indicate strongly that this process is a true involution (30). In these animals after removal of the pituitary gland, the spermatogenic cells undergo a prompt dedifferentiation and, in the terminal stage, show all of the histological characteristics of the undifferentiated epithelium of the prepubertal resting testis. In similar instances in the human testis the epithelium does not undergo a lytic degeneration but appears to have dedifferentiated as in the monkey to an indifferent resting stage

Simmonds also associated the degeneration of seminiferous epithelium with thickening of the tubular wall and suggested that the degenerative changes might be a chronic nutritional disturbance as a result of blood vessel change. Simmonds reports 80 cases with hyaline transformation and tubular degeneration of the testis, 58 of which showed general systematic arteriosclerosis. He saw testis degeneration in men in the forties with cardiovascular disease. However, many instances of hyaline transformation with tubular degeneration are found in the absence of known cardiovascular disease.

An exact causal relationship between the hyaline thickening and seminiferous destruction cannot be established In both man and monkey the two conditions are associated. As hyaline or collagenous thickening occurs the capillary bed is thrust further from the basement membrane of the epithelium. It is not impossible that the degeneration of seminiferous epithelium is the result of a trophic disturbance affecting the metabolic requirements or respiration of the sperm forming elements.

Other instances of unknown causation where all spermatogenic elements have disappeared, leaving an abundance of normal appearing Sertoli cells on a thin normal basement membrane, appear in younger men as well as aged men (6).

According to Stieve, the tubules in the aged remain the same width when sperm bearing, and have no more involutionary changes than in young

men, when there are no complications of medical importance. However, he sees that the tubules of the aged are not round but many angled. This is to be observed in our specimens when the highly refractive basement membrane thickens and throws loops in towards the lumen. This may be a result of increase in elastic fibers and decrease of collagenous fibers in the tubule wall.

One difficulty with statements in the literature is that many reports have been made from material from routine autopsy. Spangaro, for instance, differentiated two forms of senile testis—the normal senile testis which shows no essential change in advancing age and the atrophic senile testis. This is to say that many testes show no change, but are found in men of an age when senility might well occur. Stieve remarks that the changes recorded by Spangaro as occurring in the atrophic senile testis also may be seen in younger man when the testis may have been injured by general illness or disease. In our own series of traumatic deaths these changes are frequently seen in individuals who were free of any gross lesions or degenerative disease. Stieve comes to the conclusion, from a study of his accidental deaths, that the testis activity in the aged is not essentially different from that of younger men. He is, however, of the opinion that there are more broken off spermatogenic cells and a larger proportion of many nucleated protoplasmic clumps in the aged than in younger men. Careful statistical studies of fixed specimens need to be made, as these cells are readily seen in disease, as well as in the semen of younger men of reduced fertility. From a study of many specimens it is difficult to be certain that this is an age change.

Another phenomenon not mentioned by other observers may be seen in many testes, even in traumatic deaths. In these cases spermatozoa may be found in the Sertoli cells, but few mitoses are observed and every evidence of spermatogenic arrest occurs. This is not due to the well known fact that spermatogenic waves occur and various portions of tubules or testes may be resting while other areas are acting. The state of spermatogenic arrest is uniform in not only one but both testes in these cases.

An extended study on the human testis is that of Olesen (31) who examined material from 187 cases at the Institute for Forensic Medicine in Copenhagen. The age range was from 15 to 83 years. The author concludes that there is no increase in abnormal sperm heads in relation to age. There is an overall spread of 33 per cent of the cases having more than 20 per cent of abnormal spermatozoa. Also it is pointed out that the average diameter of the tubules is no different in individuals over 50 years than in those under that age. Indeed the only changes which occurred regularly in this group is "a thickening of the membrana propria, with the formation of a hyaline membrane immediately below the epithelium". This

constant finding in our own material which was reported above is thus corroborated

Interstitial cells (Leydig cells)

Any statements of the number or volume of interstitial cells are entirely subjective. No counts have been reported in the human Attempts to estimate the interstitial cell mass have not been successful. Interstitial cells are found singly or in patches among other connective tissue cells in the intertubular areas. In juvenile and atrophic conditions it is frequently impossible to distinguish the resting interstitial cell from the fibroblast of the areolar tissue.

Recent studies with the gonadotropic hormone from pregnancy urine, as well as morphological studies, indicate that the large vacuolated interstitial cell may develop rapidly from undifferentiated cells. Whether these are fibroblasts or resting undifferentiated mesenchymal cells is unknown If these cells can temporarily be increased in number at the expense of fibroblasts, it is presumed that they also can undergo dedifferentiation and resume the appearance of a connective tissue cell.

All attempts to relate the number or condition of interstitial cells to sexual activity in man have revealed nothing. In cases of homosexuality, abnormal sex drive or other psycho-pathological states no histological or cytological changes were found which were not also found in the control series of "normal" men (23).

Similarly it has been difficult to show any change except pigmentation in the interstitial cells which were associated only with age. Teem (32) has examined a large number of testes from routine autopsy material. The number of interstitial cells was estimated, not counted nor measured, and a "relative average number" secured. According to his estimates the relative average number of interstitial cells decreased in the decade 50 to 59 years.

The range of variability is so great in the human testis that a large series must be inspected to obtain the subjective impression of the spread of normality. The technical difficulties involved are discussed by Sand and Okkels (23), who devised an elaborate system for counting and evaluating the number of interstitial cells in their large series but abandoned the method as being unsatisfactory.

Stieve has taken exception to the Steinach school which thought that the interstitial cell mass increased with age. This is a misconception, as it also is in cryptorchidism, due to the shrinkage of tubules and therefore the relatively greater number of interstitial cells. Oiye (33) had previously stated specifically that he could determine no change in numbers of interstitial cells in relation to ageing.

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tative study are summarized in figs. 6 and 7. Thus it is seen that in the post-pubertal group, the Sertoli cell lipid, which first appeared at age 15, gradually increased to a maximum grading in old age. Lipid content of the Leydig cell first appeared at age 12, increased rapidly to age 17, at which maximum level it remained until age 35. From this high level the stored

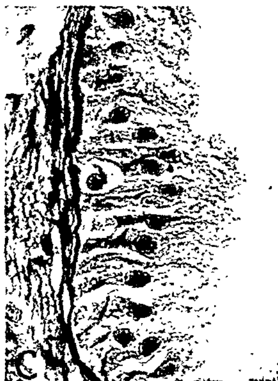


FIG 5. Sertoli cells from a tubule with few germ cells The characteristic shape of the nucleus is shown There is no demonstrable limiting apical membrane for these cells The slender crystalloids are present in several cells

fats slowly decreased throughout later maturity and old age. This curve (fig. 7) of Lynch and Scott is roughly comparable to the ketosteroid excretion curve of Hamilton and Hamilton (15). The lipids of the interstitial cells may indicate the manufacture or storage of the androgen complex, but what is the significance of the stored lipid in the Sertoli cell? Lynch and Scott discuss their findings in the light of the hypothesis of Teilum (35) that the increased lipid content of the Sertoli cell means estrogen production. Since the storage of Sertoli cell lipid increases in amount in the older age groups when androgen production is gradually reduced. Such

The Sertoli cell

At birth the testis tubule of the newborn male is usually a solid cord, filled with undifferentiated epitheliold cells. Occasionally an obvious spermatogonium may be present. Sertoli cells and spermatogonia differentiate at 2 to 4 years of age. From this time on through life the Sertoli cell is a characteristic structure within the tubule. In tubular fibrosis and other pathological disturbances of the testis the Sertoli cell may be the only cell within the tubule. Regarding this special cell type, which is one of the earliest to differentiate, and always the last to disappear we have remarkably little specific information.

The Sertoli cell is not readily recognizable in the normal testis tubule, because its cell outlines are frequently obscured by adjacent cells of the germinal epithelium. In certain conditions, where the Sertoli cell is the only, or the main, structure present more detail can be seen (fig. 5). It is a tall columnar cell, invariably based on the basement membrane with lateral cell borders clearly delimited. The state of an apical membrane is uncertain. No easily demonstrable membrane is seen, the cytoplasm appearing to be without a specific structural limitation. The oval nucleus with one or two bright nucleoli is the real diagnostic characteristic. The nucleus has a cleft or groove on its surface, appearing as does the lacing on a football.

During normal reproductive life, the maturing spermatozoa makes contact with the Sertoli cell and normal sperm heads are seen, apparently bathed in the apical cytoplasm of this sustentacular or nurse cell. It is assumed that this relationship is essential for the proper maturing of the sperm cell.

Interest in the Sertoli cell has aroused renewed interest in the last decade, and its role in all age groups is being investigated. Huggins and Moulder (34) showed that in the male dog, feminizing tumors of the testis occurred which were high in lipid content, rich in estrogen, and appeared to be a tumor composed predominantly of Sertoli cells. A Sertoli cell tumor has not definitely been recognized in man, but Teilum (35) presents evidence for a group of lipoid rich, tubular adenomas of the ovary and the testis which may prove to be in this category of known estrogen producing neoplasms.

The evidence to date has been reviewed by Lynch and Scott (36), who present new and well documented observations on the lipid content of the Sertoli cell of man in relation to age and to prostatic disease. These investigators studied the testes of 168 human males ranging from 2 months premature to 84 years of age. Histological sections, stained for neutral fats, were examined and graded as to lipid content of the interstitial cells of Leydig and the sustentacular cell of Sertoli. The data of this semiquan-

tative study are summarized in figs. 6 and 7. Thus it is seen that in the post-pubertal group, the Sertoli cell lipid, which first appeared at age 15, gradually increased to a maximum grading in old age. Lipid content of the Leydig cell first appeared at age 12, increased rapidly to age 17, at which maximum level it remained until age 35. From this high level the stored

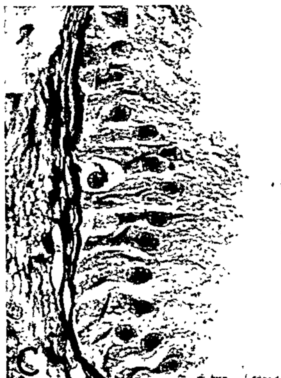


FIG 5 Sertoli cells from a tubule with few germ cells. The [illegible] the nucleus is shown There is no demonstrable limiting [illegible] cells The slender crystalloids are present in several cells.

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SERTOLI CELL LIPID

++++
+++
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10 20 30 40 50 60 70 80 90

AGE IN YEARS

FIG. 6. Chart showing the distribution in stainable lipid in the Sertoli cells of man by age in years. From Lynch and Scott (36).

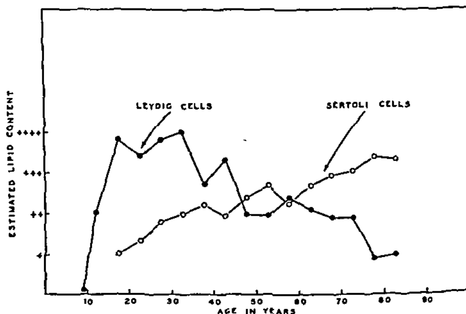


FIG. 7. Chart showing the distribution of stainable lipid in the Leydig cells as compared to the Sertoli cells in man by age in years. From Lynch and Scott (36).

excretion studies of estrogen in men as are available indicate that while estrogen is present, there is no certainty that these substances increase in later maturity or old age. Lynch and Scott consider the apparent increase in Sertoli cell lipid to show a significant correlation with phenomena associated with the process of ageing, but quite properly do not commit themselves as to the nature of the process.

Pigment and granules

Pigment is a constant finding in the genital tract of the aged male. There may be more than one type of pigment granules but the most constant are the golden brown, round granules. They occur in the interstitial cells, the efferent tubules of the testis, the smooth muscle of the prostate and the seminal vesicles. In our preparations they are very abundant in the interstitial cells of men beyond 60. In many testes of the aged, the only cells which can definitely be diagnosed as interstitial cells are those which bear pigment. The other cells in the intertubular spaces which do not have pigment may be dedifferentiated interstitial cells or they may be fibroblasts.

In the efferent tubules of many testes of older men, pigment is deposited in the stroma and can be seen both basally and apically in the epithelium The presence of much free pigment in the lumina of tubuli efferentia, and its presence in occasional semen spreads, suggest that in this respect the epithelium of the tubuli may serve as real excretory cells. In these cases, *pigment is seen in the lumina of the epididymis, but not in the epithelium.* Moore has described the increase of pigment in the smooth muscle cells of the aged prostate. Further discussion of this problem may be seen in Stieve (27) The crystalloids of Reinke are present in many interstitial cells and are found in most testes. Their function is unknown. Bukofzer (37) could find no relationship between these structures and age.

It is apparent that the widely spread misconception that a relationship exists between interstitial cells, sex drive, and age is merely another old wives' tale, which in some instances has been proved wrong, in others merely unproved.

The "Male Climacteric"

The normal cessation of menstruation in women is known as the menopause or climacteric. For some women this period of endocrine transition causes symptoms severe enough to demand medical attention.

There is some comment in the medical literature regarding a similar syndrome in man which has been known as the "male climacteric", characterized by vasomotor symptoms (hot flushes), impotence, lethargy, weakness, insomnia, etc. These symptoms may rarely be seen in older men, in association with a high titer of urinary gonadotropins and ample evidence

of testicular insufficiency. However, the number of such patients seen in large clinics is small indeed, in relation to the number of women with such symptoms or in relation to the number of men in the total population.

While testosterone therapy is of distinct value in cases of true testicular insufficiency, there is no evidence to justify consideration of the male climacteric except as a very rare syndrome, and certainly not as an inevitable epoch in the life of the ageing man (22).

Summary

A review of the morphological and functional changes in the testis which may be referred to as the ageing process presents several difficulties, the major one being a lack of precise published data.

The hormonal regulation of genital function does not cease abruptly in the male as it does in the female. However, in senescence as in puberty, the capacity of the organ to respond to an adequate stimulus, is probably more important than the loss of the hormonal activation. It remains to be shown that the involution of the genital system in age is due primarily to an endocrine deficiency. The normal variation in individuals in relation to life decades is apparently very great. The present data available on hormone assays are not abundant but indicate a general decrease in output of the sex hormones with increasing age. The appearance of the gonadotropic hormone which is so constant in the menopausal woman is far less uniform in the man and is not so clearly related to life decades.

The morphology of the seminiferous tubules of the testis serves as an indicator of endocrine adequacy. If sperm are not being formed in the tubules in males beyond puberty it may be that, lacking a history of injury or disease, the reason for failure is primarily endocrine. The influence of other factors, such as toxins, genetic constitution, vascular conditions and the autonomic nervous system, as in anxiety states, on the inhibition of sperm production are strongly suspected. On the positive side, if sperm are being formed, endocrine stability is demonstrated. Then, when spermatozoa are being formed in men of the sixties and seventies, as they are in at least half of the specimens examined, it is difficult to believe in a seriously decreased hormone level. The same statement would stand if it were shown that some of these cases with good sperm were sexually impotent.

There are morphological changes in the testes which are preponderantly associated with older age levels. These involve the thickening of the basement membrane of the seminiferous epithelium and the surrounding tunica propria. These changes may be due to disturbed vascular conditions but this has not been clearly demonstrated.

The interstitial cells of the testes very probably secrete at least a part of the androgen complex but no work has finally correlated their number or

cytological condition with age, behavior, state of the seminiferous cells or with the condition of the accessory glands.

Emphasis has been placed in this chapter on the idea that the sex hormones are required for reproduction in both sexes. The degree to which they influence sex response and behavior deserves further analysis. In this field the lore of common opinion is more generally disseminated than are the results of investigators.

The problem of the relation of male impotence to age is so complex, *and the sexual life of older men is so complicated by changes, both in* the inner physiological environment and the external social surroundings, that little can be said at the present.

In summary then, it has been stated that while the ageing process leaves its effects on the genital system of the male, it is not so uniform in its expression by chronological years as in the woman. The changes reflected in the structure of the ageing prostate appear to be more pronounced than in the testes, and more generally applicable to men of definite decades of life. The areas where age might affect the physiological and psychosexual aspects of men have been inadequately explored.

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28

METABOLISM OF AVASCULARIZED TISSUES AND CHANGES ASSOCIATED WITH AGEING

JOHN ESBEN KIRK AND PER FROM HANSEN

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Some of the avascularized tissues in the body are among the ones in which invalidating changes occur with particular frequency with age. While a considerable amount of work has been directed towards the description of the pathological anatomical senile lesions in these tissues, studies on the changes with age in the metabolism of the avascularized tissues are rather few. This scarcity of data is probably chiefly conditioned by the fact that the existing knowledge concerning the rate of metabolism and the metabolic pathways in these tissues before the onset of ageing is also somewhat limited. Since it is reasonable to believe that information gathered in this field eventually may assume the same importance for the understanding of the normal and pathological ageing processes as observations obtained through the study of tissue morphology, the inclusion in this textbook of a chapter, which summarizes the existing literature dealing with the metabolism of avascularized tissues would seem justified. It is hoped that such a review by nature of its necessary incompleteness will serve to emphasize the need for further research in this field.

The organs and tissues selected for consideration are the lens, the cornea and articular cartilage, which can all be characterized as being truly avascularized. In addition a description of the metabolism of the media of the aorta has been included in the review. Although the aortic media is not completely avascularized, the capillary supply to the luminal half or two-thirds of this section of the vessel wall is so small that with regard to metabolism this tissue may for practical purposes be placed in the same class as the lens, the cornea and articular cartilage.

The discussion of the metabolism of the individual tissues will include

not only a review of the literature dealing with the oxygen consumption as determined by in vitro experiments, but will deal also with the available data concerning the anaerobic tissue metabolism and with observations on enzyme systems accepted as being of importance for the energy transfer in the tissues. Although it is generally agreed that in vitro measurements of tissue metabolism do not necessarily represent the metabolic rates of the intact organ in the living body, such measurements nevertheless are of considerable importance in supplying information concerning the oxidative capacity of the tissue. In addition in vitro studies may yield valuable information regarding individual phases of the intermediary metabolism and especially may supply knowledge concerning the existing possible metabolic pathways of the respective tissue.

It should be recognized that one of the main features which distinguishes the avascularized tissues from vascularized organs is the fact that the avascularized tissues for their supply of oxygen and nutrients and for the disposal of waste products are dependent on a much longer diffusion way. For this reason a consideration of the histological structure of the supply route and of the diffusion coefficients for gases and crystalloids through the supply line is of great importance and should be correlated with the metabolic rate of the tissue for evaluation of the transport capacity and the margin of reserve. For such calculations the equations given by Hill (58) and by Warburg (118) may be used. At the present time, however, the lack of actually determined diffusion coefficients (71) for the tissues considered in this review prevents the performance of such calculations.

It will be apparent from the data presented in this summary that the metabolism of the avascularized tissues, as determined by in vitro experiments, is considerably lower than the figures reported for vascularized organs for which information exists. This difference does not necessarily imply that the avascularized tissues are placed in a less favorable position from a biological point of view or, as it has been expressed, that the tissues are in an asphyxiated state, since on the contrary it may be assumed that the avascularized tissues for their normal maintenance do not require as much oxygen nor as large a supply of nutrients as do vascularized tissues with a more active function. The fact that exactly avascularized tissues, like the cornea and the arteries, may be stored for several days without loss of viability would tend to support this latter point of view. On the other hand the dependency of the avascularized tissues on a long diffusion way for their metabolic supply may make these organs particularly sensitive to pathological changes occurring in the course of the diffusion route, since the damage resulting from interference with the diffusion route may be much greater.

Besides being distinguished from the vascularized tissues by a low metab-

olism and a long road of supply, the avascularized tissues to be considered in this summary may presumably be characterized as being from a functional standpoint in an approximately steady state. The metabolic demands of these tissues therefore probably do not change much from time to time, as do the requirements of a contracting muscle compared with a resting muscle and the oxygen need of a secreting gland contrasted to that of the non-secreting organ. Since the functional demands of the avascularized tissues would seem to be merely physical and since they are never called upon to supply a sudden expenditure of work (with the possible exception of the smooth muscle cells in the aortic wall), it would seem natural to regard these tissues as being not only in a metabolic steady state but also in a metabolic resting state. Both the lens, the cornea, articular cartilage and the arterial wall have the feature in common that they are in contact on one or two surfaces with a nutrient fluid. The significance of this relation will be considered in connection with each of these structures, but it should be mentioned that this arrangement is not found in the case of some other avascularized tissues, for instance the cartilage of the external ear and the tendons.

From a technical point of view the provision of quantitative data for the metabolism of avascularized tissues is on the whole associated with much greater difficulties than is the case with the examination of vascularized tissues. Thus the procedure employed in the study of the kidney, heart and brain of comparing analyses of the blood of the afferent and efferent vessel is not applicable, and even the conventional in vitro studies with the Warburg (118) apparatus cannot be conducted with the same ease nor with the same assurance of reasonable accuracy. This is due to the fact that, in order to obtain measurable excursions on the manometers, experiments extending over many hours are necessary, and under these circumstances infection of the reaction flasks is likely to occur if the strictest precautions are not observed. Also the influence of slight temperature changes and of barometric changes causes a much more serious disturbance than is the case in experiments with rapidly respiring organ slices or homogenates. On the other hand, the longer viability of the avascularized tissues makes the performance of long experiments possible, and for the reasons outlined above it is reasonable to assume that the conditions for the avascularized tissues in the in vitro experiments more closely depict the conditions in vivo than do in vitro studies performed with muscular and glandular tissues.

In the selection of the data from the literature on the metabolism of avascularized tissues the authors have been confronted with the difficulty that information is usually lacking concerning precautions taken to avoid infection of the tissue samples. Since the present authors in their own

studies have been impressed with the considerable errors which may arise from even slight bacterial contamination, some reservation must be made regarding the validity of the quantitative metabolic data presented.

The Lens

Structure and measurements

The human lens has a diameter of 8 to 9 mm. Its thickness increases from 3.6 mm. at the age of 20 years to 4.2 mm at the age of 80 (33, 61, 105) and the volume of the organ from 160 to 240 cu. mm. between youth and old age (33, 110). This increase in thickness and in volume is caused by the continuous growth of the lens fibers throughout life. The growth affects only the cortex of the lens, which both on the anterior and posterior surface increases in thickness from about 0.4 mm. in young individuals to approximately 0.8 mm. at the age of 80 (61). In contrast to the cortex no certain change with age has been observed in the size of the nucleus of the lens, which in the human possesses an average thickness of 2.8 mm. (61) (range 2.2 to 3.6 mm.). The increase in thickness and volume of the lens with ageing is a feature of considerable gerontological importance, since this augmentation results in a longer diffusion way for the supply of the central portion of the organ.

The structureless lens capsule surrounding the lens at the anterior pole in young individuals has a thickness of 11 μ, but at the posterior pole is much thinner, 3 to 4 μ (104). The capsule increases in thickness with age, the anterior capsule in 20 to 39 year old individuals being on the average 11 μ and in persons aged 40 to 70 years, 14 μ. The height of the lenticular epithelium, underlying the anterior capsule, is 5 to 10 μ, the epithelium undergoes a decrease in height with advancing years (33).

In connection with the considerations about the metabolic transfer between the lens and its surroundings it should be noted that the two surfaces of the lens are different in nature; whereas the anterior surface possesses an epithelial layer, the posterior surface lacks such a structure.

Supply routes

The lens receives its supply of oxygen and nutrients from the humor

change of the intraocular fluid and its various components has not yet been established, but considerable progress has been made in this field in the last few years especially through the investigations by Duke-Elder and his associates. On the basis of these studies (34) a rapid rate of transfer

of water in both directions between the blood and the humor aqueous has been demonstrated, which confirms the earlier studies by Kinsey, Grant and Cogan (65) performed with the use of heavy water. In the rabbit eye the transfer by diffusion in and out of the anterior chamber amounts to 50 cu. mm. per minute, which corresponds to a replacement of half of the humor aqueous every 2.7 minutes. Similar values have been found by Cagianut, Heusser and Eichenberger (25) for the human eye. In addition to the exchange of water by diffusion an actual drainage of fluid takes place through the canal of Schlemm and the aqueous veins. In the normal eye approximately 1 per cent of the fluid in the anterior chamber drains away per minute (34, 46, 64), a flow amounting to about 2 cu. mm. per minute for the human eye (34, 46).

By sudden freezing of the eye during diffusion experiments new knowledge has recently been acquired concerning the way of entry of substances into the eye (35); in this manner it could be demonstrated that whereas some compounds enter the vitreous body predominantly by the way of the ciliary body and diffuse backwards towards the posterior pole of the eye, other substances, including glucose, can enter the vitreous body rapidly from all parts of its perimeter.

The concentration of glucose in the various compartments of the eye surrounding the lens has been the subject of several studies, which are all in essential agreement. In the recent investigations by Davson and Duke-Elder (29) on the eyes of cats, average glucose concentrations in the aqueous of 83 mgm. per cent and in the vitreous of 57 mgm. per cent were found with an arterial plasma glucose concentration of 108 mgm. per cent. The lower value observed in the aqueous can probably be ascribed to glucose uptake by the lens and the cornea and that of the vitreous to metabolic requirements of the lens and the retina. In the excised incubated eye the glucose concentration of both the aqueous and the vitreous have been found to decrease steadily.

The oxygen content of the humor aqueous of the rabbit eye was measured in 1922 by de Haan (50), using the Krogh microtonometer. The oxygen tension values found corresponded quite closely to those of venous blood.

The permeability of the lens capsule for crystalloids was first proved by Bence-Jones (13, 14) in 1865, who, after subcutaneous injection of lithium salts, was able to demonstrate lithium by spectrum analysis in the superficial parts of the lens as early as ten minutes after the injection. The subject of capsular permeability was later studied by Friedenwald (43), who showed that the capsule is permeable for both salts and glucose. As mentioned in the introduction, investigations on the diffusion rates of gases through lenticular tissue have not yet been reported.

Extensive studies on the passage of the radioactive isotope of phosphorus,

P^{32}, from the blood through the anterior uvea and aqueous into the lens were published by Palm (89) in 1948. In these experiments labelled phosphate was injected intraperitoneally into living rabbits, the animals were killed at different times after the injection, their eyes extirpated, and the lens removed for analyses, which revealed to what extent the phosphate in the various phosphorus-containing compounds in the lens had been replaced by newly administered phosphate. The data showed that a short time after the intraperitoneal injections newly introduced phosphate was found inside the lens where it was rapidly converted into an organic form. Additional investigations on isolated lenses placed in labelled phosphate solution revealed that the phosphate penetrated into the lens through both the anterior and posterior surface with about equal speed. A difference was noted, however, with regard to the incorporation of the phosphate into organic phosphate fractions; thus the anterior part of the lens was found to contain twice as high a concentration of phosphate in an organic form as the posterior section. Furthermore, the compounds representing the first stage of carbohydrate phosphorylation were found only at the anterior surface of the lens, a fact which makes it natural to associate the lenticular epithelium with this metabolic function.

As mentioned above, the lens capsule increases in thickness with age. As might have been expected, the important problem of the effect of age on capsular permeability has received much attention since this subject is closely related with discussions on the correlation between capsular permeability and the development of cataract. The investigations by Friedenwald (43) performed on cows' lenses show a significant decrease in the permeability of the capsule with age. The observations on capsules from cataractous lenses fall, however, approximately within the limits of variation for normal adult lenses.

In the opthalmological literature some reports are available on the effect of interference with the nutrient supply of the lens. After ligation in the cat of one of the long posterior ciliary arteries and some of the short ciliary arteries Wagenmann (116) only in a single experiment observed cataractous changes developing during the life of the animal; when the whole arterial supply to the eye was interrupted, gangrene of the bulb regularly followed.

The investigations by Wagenmann in which the local blood supply to

posed of 5 per cent oxygen and 95 per cent nitrogen. As a result of such anoxia, opacities of the lens occasionally developed. These turbidities were found to regress after subsequent exposure of the rats to atmospheric air. The observations by Biozzi were later confirmed by Bellows (12).

In this connection in vitro studies by Friedenwald (43) in 1930 should

be mentioned. In these studies normal lenses were placed in sterile salt solution at body temperature, but no provisions were made for supplying the lenses with nutrients or for removal of metabolic waste products. It was found that under these circumstances cataractous changes developed which both on slit lamp and on histological examination showed great resemblance to spontaneous senile cortical cataracts.

Enzyme systems and metabolism of the lens

The lens contains all the enzymes necessary for the breakdown of carbohydrates; the glycolytic system is inhibited by fluoride and by freezing of the lens tissue (73). The presence of enzyme systems capable of dehydrogenating lactic, fumaric, malic and succinic acids has also been demonstrated (1, 2, 3, 4); according to Ahlgren, however, (4) succinic dehydrogenase is not present in the lens. The existence of the dehydrogenases in the lens makes it possible for lenticular tissue to reduce methylene blue (4); no reports seem, however, to have been published concerning a stimulating action of methylene blue on the oxygen uptake.

The further pathways for the oxidation by lens tissue have been the subject of considerable investigation (37, 38, 57) and speculation. In 1945 Herrmann and Moses (57) succeeded in preparing from fresh bovine lenses a system which would oxidize hydroquinone more rapidly in the presence of cytochrome c than without it, for which reason they suggested that cytochrome oxidase is present in the lens. On the basis of this observation Ely and Robbie (37) attempted to demonstrate the presence of cytochrome c in homogenates of beef lenses, using the spectrophotometric method of Rosenthal and Drabkin (103). Although recovery procedures with added cytochrome c showed that this method would measure amounts of cytochrome c in excess of 20 µg. per gram, no cytochrome could be detected in the homogenates, this failure indicating either that cytochrome c is absent from the lens or is present in quantities less than 20 µg. per gram.

In spite of the fact that it has thus not as yet been possible to demonstrate cytochrome c in the lens, the ability of cyanide to inhibit oxygen consumption by lenticular tissue seems well established. This inhibition was already shown in the publication by Herrmann and Moses (57) in 1945 and is well illustrated through the experiments by Ely and Robbie (37) in 1950. In these later studies the inhibition valued 50 per cent at 10^{-4} M cyanide concentration and 91 per cent at 10^{-2} M concentration. These results show that the oxidative metabolism of the lens is for the greater part dependent on a cyanide sensitive hydrogen carrier system, the chemical nature of which is not at present known.

The role of glutathione and ascorbic acid for the oxidative metabolism of the lens has likewise received much attention. Thus it has been shown

that if glutathione is removed from the lens by dialysis (1, 2, 47) the power of oxygen consumption is lost, but this power may be restored by addition of glutathione to the medium. The position of glutathione in the metabolic chain is, however, unknown. It is of considerable interest that ascorbic acid is present in the lens (39, 52, 53, 73, 85, 119) and in the humor aqueous in much higher concentrations than in the blood, but the eventual function of this compound in the intermediary metabolism of lenticular tissue also remains uncertain. Both glutathione and ascorbic acid are found in somewhat higher concentrations in the cortex than in the nucleus (52). The concentrations decrease markedly with age (52, 85), and these compounds are usually absent from lenses that have undergone cataractous alterations (39, 85, 119, 120).

The effect of age on the enzyme systems responsible for the carbohydrate breakdown has been the subject of valuable investigations by Muller (84) and by Süllmann (112). In the studies by Muller (84) extracts were prepared from young and old cattle lenses, and the ability of such extracts to split hexosediphosphate to trioses measured It was found that the activity of the preparations from old lenses on the average was only about half as great as the activity of extracts from young lenses, and the interesting observation was further made that old cattle lenses, which had a yellow nucleus, possessed the lowest enzymatic activity. The ability of extracts from old lenses to synthesize organic phosphorus esters was likewise found much reduced. The simple phosphatase activity, as tested with glycerophosphate as substrate, appeared, however, to be unchanged with age.

In the investigations by Süllmann (112) the rate of phosphorylation after addition to lenticular extract of monohexoses was made the subject of a special study. It was found, in good agreement with Muller's observations, that the intensity of phosphorylation in extracts from old cattle lenses was only about half as great as the activity displayed by extracts from young lenses and that in preparations from cataractous lenses the observed phosphorylation was minimal.

As first shown by Bakker (7, 8) in 1939 both human and animal lenses contain an unusually high concentration of the enzyme carbonic anhydrase, the activity of lens tissue being equal to or higher than that of the blood corpuscles. The concentration (8) is especially high in sheep, ox, cat and dog lenses, but rather low in the lens of the pig. Just as the enzyme present in the red blood cells the lenticular carbonic anhydrase will catalyze both the hydration of carbon dioxide and the dehydration of carbonic acid (9).

Whether the hydrating or the dehydrating catalysis is the important function (9, 48) of the enzyme in lens tissue is difficult to decide until more is known about the end product of tissue metabolism in the lens. If carbonic acid is formed in large amounts a catalysis of the dehydration of carbonic acid would be a useful mechanism

in facilitating the elimination of carbon dioxide from the lens, since the diffusion of carbon dioxide is more rapid than that of carbonic acid. If, on the other hand, the actual product of the cell respiration is carbon dioxide, the enzyme would presumably retard the elimination of carbon dioxide The significance of such retardation is difficult to comprehend, although it could be postulated that the accumulation of carbon dioxide might be of importance for creating a local pH optimum for some enzymatic function (6) or might constitute a limiting factor for the oxidative processes

As shown by Bakker (7, 10) the concentration of carbonic anhydrase in cataractous lenses is decreased to a degree corresponding to the turbidity of the lens. In several cases of mature cataract no trace of the enzyme could be detected.

The rate of oxidative metabolism of the lens has been the subject of several studies, the earliest of which dates back to 1923 (80). In all the investigations a measurable oxygen uptake has been reported for the noncataractous lens. In evaluating the significance of such finding the question arises to what extent the observed oxygen consumption represents actual tissue metabolism and how great a part of the oxygen uptake is conditioned by autooxidation of ascorbic acid and glutathione, which, as mentioned, are present in high concentrations in the normal lenticular tissue. Although some of the earlier investigators (73) are quite aware of the problem of autooxidation, no procedures for distinguishing this oxidation from the cellular oxidation have been offered.

That an autooxidation of easily oxidizable substances probably takes place during the in vitro experiments is suggested by de Haan's (50) observation in 1922 of a considerable oxygen consumption by samples of the humor aqueous. The low or absent oxygen consumption by cataractous lenses might similarly be explained by the low concentration in or absence of ascorbic acid and glutathione from such lenses. A similar argument might apply to the observation by Goldschmidt (47) and by Adams (1, 2) that removal of glutathione from the lens by dialysis causes a loss of oxidative power and that the replacement of this compound restores the oxygen consumption to the lens. In indirect support of the existence of an actual, cellularly conditioned, oxygen uptake by the lens is, however, in the opinions of the authors, the fact that the nucleus of the lens has a very low or no oxygen consumption, although it possesses a relatively high ascorbic acid and glutathione concentration. In connection with the considerations offered here concerning the oxidative metabolism of the lens it should be noted that no measurements seem to have been published of carbon dioxide production by lenticular tissue.

In the comparison of the reported data for the oxygen uptake by the lens a distinction must be made between Q^{O_2} measurements performed on intact lenses and determinations carried out on disintegrated lens tissue.

In many of the experiments separation of the lens fibers has been performed intentionally, for instance, for the purpose of determining the oxygen consumption by the nucleus and the cortex separately, whereas in other experiments the disintegration of the lens occurred accidentally by rupture of the capsule during the shaking of the lens in the Warburg flask. As noted already by Mashimo (80) and confirmed by many later investigators, such occurrence is regularly followed by a notable increase in the oxygen uptake (36, 73, 109).

The measurements of the oxygen uptake by intact rabbit lenses are on the whole in good agreement and show an oxygen consumption of between 2.5 and 10 cu. mm. oxygen per lens per hour, corresponding to Q^{O_2} values of about 0.05 to 0.10. In carefully conducted studies in recent years on a larger number of rabbit lenses, Ely (36) similarly obtained a mean Q^{O_2} value of 0.09 (range 0.05 to 0.21). It may be concluded from these results that the oxygen consumption by the lens is only about 1/100 to 1/200 of the respiration value of liver and kidney tissue.

Determinations of the oxygen uptake by the various parts of the lens have been performed by Schmerl (109), Kronfeld (72, 73), Campos (26) and Ely (36), all working with rabbit lenses, and by Pignalosa (92) on the bovine lens. In the studies by Campos and by Ely no oxygen consumption could be recorded in experiments performed with the isolated lens capsule, whereas Pignalosa gives a mean Q^{O_2} value of 0.12 for this structure. The discrepancy between these findings may be due to a species difference or may be conditioned by the completeness with which the capsule was separated from the cortical structure, since as demonstrated by Ely, the adherence to the capsule of even small amounts of lenticular epithelium will result in a measurable oxygen uptake by the sample

The studies on the oxidative metabolism of the nuclear part of the lens are of particular interest because of the dependence of this section of the organ on a relatively long diffusion way. The first measurements on the isolated rabbit nucleus were made in 1928 by Schmerl (109), who in experiments conducted over two hours was unable to register any oxygen uptake. Similar negative results were obtained by Field, Taintie, Martin and Belding (40) and by Ely (36), whereas Pignalosa (92) reported a mean Q^{O_2} value for the bovine lens nucleus of 0.02 (range 0.00 to 0.07). Although the question whether the nucleus of the lens possesses any oxidative metabolism or not cannot as yet be considered as definitely settled, it seems justified to conclude that the respiration of the nucleus, if present at all, must be small.

Concerning the oxygen uptake by the cortical part of the lens all investigators are agreed that a measurable oxygen consumption regularly can be recorded in in vitro studies. Thus in the investigations by Campos (26)

a mean Q^{O_2} value for the teased rabbit cortex of 0.49 was found, and in the experiments by Ely (36) an average value of 0.145. For the isolated beef cortex Q^{O_2} figures of 0.53 (range 0.33 to 0.78) (Pignalosa (92)) and 0.168 (Ely (36)) have been reported. It is possible that the difference in observed oxygen consumption in these two latter studies has been conditioned by the degree of separation and teasing to which the lenticular fibers had been subjected.

The fact that the intact lens possesses an oxidative metabolism lower than that of disintegrated lens tissue has been interpreted to indicate that the supply of oxygen or of substrate to the lens under normal conditions is not maximal. Since the diffusion coefficients for oxygen through the lenticular capsule and lens substance are not known, it is not possible to calculate with certainty how thick a layer of the lens can be supplied with oxygen by diffusion. The finding that the isolated nucleus by in vitro experiments shows no oxygen uptake or only a very low one suggests that the central portion of the lens for the larger part of its energy producing processes is not dependent on oxidation. It should be pointed out, however, that the higher Q^{O_2} values measured for disintegrated lens tissue could be explained merely by the fact that in such preparations the contact surface between the tissue and the oxygen and substrate is much larger (26).

Investigations on the oxygen consumption by normal human lenses are not available, but measurements have been performed on human cataractous lenses. The first such measurement, in a case of hypermature cataract, was performed by Schmerl (109) in 1928 and showed the complete absence of an oxygen uptake. A more extensive study on human senile cataractous lenses was published in 1939 by Orzalesi (88). As seen from table 1, a zero oxygen consumption was also occasionally observed by Orzalesi, but in several other instances a small but definite oxygen uptake was found. This uptake is believed by Orzalesi to be conditioned by the persistence in some cataractous lenses of a certain number of clear and metabolizing lens fibers. Since the lenses were removed by extracapsular extraction the values represent the oxygen consumption of disintegrated lens tissue.

The formation of lactic acid by lenticular tissue was first demonstrated by Kronfeld and Bothman (73) in 1928, and the glycolytic ability of the lens was later confirmed by Cohen and Killian (28), Michail and Vancea (82, 83) and Campos (26) working with rabbit lenses, and by Pignalosa (92) studying the bovine lens. In all the investigations the manometric technique of Warburg was used. For the intact rabbit lens $Q_{M}^{N_2}$ values ranging between 0.50 and 1.00 were found.

In the studies by Pignalosa (92) on the bovine lens the rate of glycolysis by the separated portions of the lens was determined. The measurements,

performed on 10 lenses by the Warburg manometric method, showed a mean Q^{n2}_{a} value for the capsule of 0.74 (range 0.50 to 1.19), for the disintegrated cortex of 0 59 (range 0.36 to 1.19) and for the teased nucleus of 0.51 (range 0.33 to 0.74). It will be seen from these figures that the glycolytic ability of disintegrated lens tissue was found to be approximately the same as that of the intact lens, and it will further be noted that no great difference exists between the glycolytic values for the cortex and for the nucleus. This latter fact is particularly interesting in view of the demonstrated marked difference in the rate of oxygen consumption between these two portions of the lens. These findings give further support to the assump-

TABLE 1

The oxygen uptake by human lenses with senile cataract (88)

Number	Type of cataract	Q^{O_2} values
1	Sclerotic	0.16
2	"	0.08
3	"	0 06
4	"	0.16
5	"	0.01
6	Soft	0 20
7	"	0.00
8	"	0.26
9	"	0 16
10	"	0.11
11	"	0 18
12	"	0 08
13	"	0 09
Mean		0 12

tion that the nucleus is chiefly dependent on glycolysis for its energy supply. In this connection it would be of value to know if any metabolic interdependence exists between the nucleus and the cortex in a manner similar to that which has been postulated to be operating between the stroma and the epithelium of the cornea (see section on corneal metabolism). To the knowledge of the authors such interdependence has not been suggested in the case of the lens or subjected to experimental investigation.

Except for the studies by Müller (84) mentioned in the introduction in the discussion of the enzyme systems of the lens, no investigations have been reported concerning the effect of age on the rate of glycolysis. Measurements have, however, been performed by Orzalesi (88) on human senile cataractous lenses, and these determinations are of considerable significance. The results of Orzalesi's studies are presented in table 2.

It will be seen from the table that a glycolytic activity is occasionally absent in human cataractous lenticular tissue and that in other instances the rate of glycolysis is small. Although data concerning the normal rate of oxygen uptake and of glycolysis by human lens tissue are not available, the very low values found by Orzalesi suggest that senile cataractous changes in the lens are associated with a reduction of both the oxidative and anaerobic metabolism of this organ.

TABLE 2

The rate of glycolysis by human lenses with senile cataract (88)

Number	Type of cataract	$Q_G^{N_2}$ values
1	Sclerotic	0.06
2	"	0.04
3	"	0.08
4	"	0.09
5	Immature soft	0.33
6	" "	0.23
7	Mature soft	0 00
8	" "	0 00
9	" "	0.00
10	" "	0 09
11	" "	0.06
12	" "	0.11
13	" "	0.10
14	" "	0.05
15	" "	0.12
Mean		0.09

Cornea

Although no studies appear to have been performed on the effect of ageing on the metabolism of the cornea, a brief review of the corneal metabolism in non-aged subjects will be included in this chapter, since the available data would seem to constitute a valuable basis for gerontological investigations in this field. The cornea does not usually become the site of invalidating senile changes; the frequent occurrence of arcus senilis with advancing years would, however, suggest a change in tissue metabolism with age.

Structure and measurements

The cornea in the human adult eye has a diameter of 12 mm. and a thickness of 0.8 to 1.15 mm. (33, 114). The weight of the fresh organ is about 180 mgm. (33). It consists of five layers, the thickness of each of

which is approximately as follows: corneal epithelium, 50 to 100 μ, Bowmann's membrane, 10 to 13 μ; corneal stroma, 0.7 to 0.9 mm.; Descemet's membrane, 5 to 7 μ; and corneal endothelium, 5 μ. The corneal epithelium possesses at least five layers of cells, whereas the endothelium is single layered. The stroma makes up 90 per cent of the thickness of the cornea; it consists of about 60 lamellae, each 1.3 to 2.5 μ thick.

From the point of view of corneal metabolism the distribution of cells between the epithelium and the stroma is of interest. Thus it has been found in measurements (54) on bovine corneas that whereas the number of cells in the epithelium is about 70 million, the stroma contains only 25 million cells. This means that the cell content of the whole epithelial layer is two to three times greater than that of the stroma, although the weight of the corneal epithelium is only about one-sixth to one-ninth of that of the stroma.

Supply routes

The three supply routes for the cornea are the tears, the pericorneal capillary network and the humor aqueous. The relative importance of each of these three supply ways has, however, not as yet been established.

In 1936 Kohra (70) in animal experiments showed that ligation of the ciliary arteries within three to four hours was followed by the development of opacities in the deep layers of the cornea, while interruption of the pericorneal circulation did not cause such changes On the basis of these findings Kohra concluded that the supply of the cornea through the humor aqueous was the most important. In contrast to these observations, Potts and Johnson (94) in a recent study, in which the rate of entry of various labelled ions (phosphate, sodium, iodide, cerium) from the blood stream into concentric circular sections of the rabbit cornea was investigated, noted a significantly higher concentration of these substances in the peripheral regions of the cornea than in more centrally located parts. On the strength of these observations Potts and Johnson suggested that the limbal vascular plexus plays a predominant role in the supply of the cornea, and they further supported this contention by demonstrating that damaging of the pericorneal capillary network through application of silver nitrate resulted in a marked decrease in the speed of entry of the ions into the cornea from the blood stream. In a similar study with radioactive phosphate, Palm (90) in radioautographs of the cornea was unable to detect any difference in radioactivity between the various parts of the organ. In this connection it should be mentioned that attempts have been made by Duane (32) to determine in the bovine and rabbit cornea whether a gradient of respiration exists from the periphery of the organ to the center;

the results of these measurements, performed on punched out pieces of the cornea have, however, been inconclusive because of the technical difficulties associated with the determination of differences in the respiratory rate of an organ with a comparatively low oxygen consumption.

Evidence for the importance of the tears, which normally have a glucose content of 60 mgm. per hundred cc. for the supply of glucose to the cornea has recently been provided through experiments by Herrmann and Hickman (54), who irrigated the surface of surviving beef corneas with ordinary Ringer's solution and with Ringer's solution containing 0.1 per cent of glucose. The experiments were conducted at room temperature and lasted for periods of twenty hours, one drop of the solution being brought in contact with the cornea every ten seconds. It was found that irrigation with the glucose containing Ringer's solution sufficed to keep up a normal lactic acid concentration of the cornea, whereas the lactate content of the cornea was depleted in those experiments in which the unsupplemented Ringer's solution was employed.

Enzyme systems and metabolism of the cornea

Both the epithelium and the stroma contain the enzyme systems necessary for the glycolytic breakdown of glucose (54), and in the corneal epithelium the concentration of adenylpyrophosphate fractions is as great as or greater than that found in the liver. The glycolytic process can be inhibited by fluoride and iodoacetate (54, 56). The epithelium further possesses lacticodehydrogenase and in addition contains a cytochrome-cytochrome oxidase system (56, 57), the existence of which was first reported in 1942 by Herrmann and Hickman (56). Demonstration of cytochrome c by spectrophotometric procedure does not, however, seem to have been made. Further studies on this cyanide-sensitive hydrogen transport system in the rabbit cornea were published in 1947 by Robbie, Leinfelder and Duane (96), who noted a 50 per cent inhibition of the oxygen consumption with a cyanide concentration of 10^{-4} M, and 93 per cent inhibition in solutions of 10^{-3} molarity.

While both the epithelium and the stroma are capable of glycolytic breakdown of glucose, the oxidative metabolism of the cornea is chiefly confined to the epithelium and the endothelium. In the investigations by Herrmann and Hickman (54) no demonstrable respiration was found by the stroma, but a slight oxygen uptake by this layer of the cornea has recently been reported by deRoetth (98).

The existence of a metabolic interaction between the stroma and the epithelium was postulated in 1948 by Friedenwald (44) and Herrmann and Hickman (54, 55), who noted that an accumulation of lactic acid occurred in the stroma of beef corneas when a separation between the

stroma and the epithelium had been effected through the action of mustard gas. On the basis of this observation they advanced the interesting contention that under normal circumstances a transfer of lactic acid takes place from the stroma to the epithelium, which latter structure is then responsible for the oxidation of both the lactic acid formed in the epithelium itself and of that provided by the stroma.

The presence of a small amount of carbonic anhydrase in the cornea of rabbits was reported by Bakker in 1941 (8).

The first studies on the corneal metabolism using the Warburg technique were published by Kohra in 1936 (70). A strong impetus for further studies in this field was provided during the second world war by the desirability of investigating the effect of war gases on the corneal metabolism (Friedenwald (44); Herrmann and Hickman (54, 55)) and a further impulse has existed during the last few years in connection with attempts at storing excised human corneas for transplantation purposes.

A review of the reported data for the oxygen consumption of the entire rabbit cornea shows Q^{O_2} values ranging from 0.46 to 2.09 (32, 98), whereas for the whole beef cornea average Q^{O_2} figures of 0.60 (98) and 0.73 (54) have been found. These values represent an oxygen uptake about 10 to 20 times lower than that of liver and kidney tissue, but about 10 times higher than the Q^{O_2} figures observed for the intact lens. For the rabbit cornea oxygen consumption values of the same order of magnitude have been observed (98), and according to Duane (31) this is also the case for the human cornea. As shown by Herrmann and Hickman (54) the Q^{O_2} values for the isolated corneal epithelium range between 4.0 and 8.0. In the few instances in which the respiration of the corneal endothelium has been measured it has been found to be as high or even higher than that of the epithelium per unit of weight. While Herrmann and Hickman (54), as mentioned above, were unable to record any oxygen uptake by the stroma, the low Q^{O_2} value of 0.085 was recently reported by deRoetth (98) for this structure.

The rate of anaerobic glycolysis of the cornea has been studied both by the manometric method of Warburg and by direct chemical analysis of the produced lactic acid. The $Q_{E}^{n_2}$ values for the rabbit cornea were found by Kohra (70) to be 2.32 for the whole organ, 8.0 for the epithelium and 1.32 for the stroma. In the investigations in the last few years by Herrmann and Hickman (54) and by deRoetth (99) on the bovine cornea a somewhat lower rate of glycolysis has been measured, the mean $Q_{E}^{n_2}$ for the whole cornea being 0.70 to 0.85 without addition of glucose and 1.40 to 1.75 in experiments with glucose addition. For the isolated epithelium (99) the corresponding figures were 3.5 and 4.4 and for the stroma (99) alone 0.11 and 0.25.

Articular Cartilage

Structure and measurements

In the human adult the hyaline articular cartilage covering the joint surfaces has an average thickness of 1.2 mm. (15). The thickness increases with advancing years and in pathological cases the cartilage may become much thicker. The ground substance, containing collagenous fibers, forms a solid mass, separating the small cavities in which the cartilage cells are enclosed.

The number of cells in articular cartilage diminishes markedly with advancing years. Thus it was found by Wagoner, Rosenthal and Bowie (117) in studies on the metacarpal and metatarsal joints of cattle that the cell content per cubic millimeter of cartilage in calves was 133,000, in adult animals 47,000, and in old animals 34,000.

Supply routes

The two supply routes for the articular cartilage are the synovial fluid and the underlying bone. The capsular blood vessels extend to the periphery of the articular surface and here form a particularly rich arterial network (42). Lymph vessels are normally found in great number just below the synovial endothelium and in the subsynovial tissue (74).

No observations seem to have been published concerning changes in the periarticular blood vessels during normal ageing. The subendothelial and periarticular lymph vessels have, however, been reported to become less numerous with age (74) and in human atrophic arthritis have been found greatly reduced or absent (74).

Of the two supply ways for the articular cartilage, the nutrition from the synovial fluid would seem to be the most important; this fluid is in contact with the greater part of the articular surface. It has been found by Ito (62) and Strangeways (111) in experiments on rats, cats and rabbits that excised pieces of cartilage placed in the free joint cavity will retain their vitality for a long period of time, the cartilage cells in the loose bodies even in some instances showing proliferation. That the synovial fluid also in human individuals is able to sustain a sufficient nutrition of loose cartilage bodies was proved by Fisher (41) and Bywaters (24) who examined loose pieces of cartilage removed from the joints of patients who had suffered traumas of the joints weeks or months previous to the surgical removal of the free cartilage bodies. In these loose bodies the cartilage cells on histological examination usually showed normal staining properties. Since it has thus been shown that the synovial fluid can nourish loose articular cartilage, it may be presumed that it is capable of the same nutrient function for attached cartilage.

The important supply of the joint cartilage from the synovial fluid brings up the subject of the formation and rate of removal of this fluid. Concerning this question no quantitative data are available either in the case of young or old subjects. It would, however, appear that the periarticular *circulation is of importance for maintaining the nutritive supply of the* synovial fluid. Thus Wollenberg and Preiser (124) were able to show in animal experiments that interruption of the periarticular arterial circulation produced necrosis of the articular cartilage, followed after six months by degenerative osteoarthritis. It should be noted, however, that in osteoarthritis in human individuals an increase rather than a reduction in the number of periarterial blood vessels is usually found (42), at least in the earlier stages of the disease, so that it is rather unlikely that an impairment of the blood supply through the larger articular arteries constitutes an etiological factor in the spontaneously occurring disease.

The observations on the significance of the adjacent bone tissue as a supply route for the articular cartilage are in good agreement and reveal that this supply is relatively unimportant. Thus infarction and subsequent necrosis of the bone has no effect on the cartilage (86). Furthermore, transection (87) of the bone just below the cartilage causes no macroscopic changes in the appearance of the cartilage. It should be mentioned, however, that histological examination of the cartilage after such section will reveal a lack of stainability of the nuclei in the cells of the basal layer so that it must be assumed that the lowermost layer of the articular cartilage receives some nutrition from this side.

No studies are available on the diffusion rates of gases through cartilage. Investigations on the diffusion rates of various crystalloids have, however, been performed by Harpuder (51), using joint cartilage from human autopsy material. In these studies portions of cartilage were sealed into the bottom of an extraction cylinder by means of solid paraffin. A known amount of isotonic sodium chloride solution was placed in the cylinder, which was lowered into a beaker containing a solution of the crystalloid under investigation, and the transfer of cations and anions determined in this manner for diffusion periods of forty-eight to seventy-two hours. On the basis of such experiments, Harpuder concluded that the diffusion rates of salts and glucose in human cartilage are rather small.

Enzyme systems and metabolism of cartilage

Cartilage contains all the enzyme systems necessary for the glycolytic breakdown of carbohydrates (79). As it might be expected, this system is inhibited by fluoride and iodoacetate (18, 24, 59). Cartilage further possesses a dehydrogenatic enzyme system; this was first demonstrated in 1932 by Kuwabara (75), who showed that costal cartilage of calves and rabbits

and sternal cartilage from chickens were able to decolorize methylene blue under the conditions of the Thunberg technique.

The capacity of the dehydrogenatic enzyme system in cartilage can be evidenced in manometric studies through the marked increase in oxygen uptake (24, 59), usually 5 to 20 fold, which follows the addition of methylene blue to cartilage preparations. A similar, although more moderate stimulation of the respiration of cartilage, may also be seen after addition of 2:4-dinitro-o-cresol (59). Among the dehydrogenases succinic dehydrogenase seems to be present in small concentrations (101).

In contrast to the considerable dehydrogenatic capacity of cartilage, the oxygen activating component of the tissue respiratory system is inconsiderable and the low activity of this part of the metabolic chain seems to be responsible for the low spontaneous oxygen consumption of cartilage, this last stage of the tissue metabolism apparently representing the bottleneck of the system. In this connection it should be mentioned that only traces of cytochrome c have been demonstrated by spectrophotometric studies of calf cartilage (79). The importance of the large potential dehydrogenatic capacity of cartilage, as evidenced by dye stimulation of the respiration in the face of a low oxygen activating component of the respiratory system is difficult to comprehend, but this combination certainly is an interesting feature in the enzymatic arrangement of this tissue.

Both the intensity of the aerobic and anaerobic metabolism of cartilage seems to be quite closely correlated with the number of cartilage cells in the tissue. Thus it was found by Bywaters (23, 24) that the glycolysis by fetal rabbit cartilage was ten times higher than that of adult tissue, and a chondroma showed a glycolysis and a respiration 30 and 60 times higher than that of normal cartilage. In agreement with these observations it was further found (24) that the superficial layer of articular cartilage from the horse, having a cell content of 20,400 per milligram of tissue, showed a Q^{n2}_{s} value of 0.278 to 0.284, or twice as high as the value for the deeper layers (0.113 to 0.152) in which the cell content was only 10,400 per milligram. The correlation between the rate of glycolysis and the number of cartilage cells has been the subject of a detailed study by Rosenthal, Bowie and Wagoner (100).

The results of determination of the spontaneous oxygen uptake by cartilage from non-aged subjects show considerable difference between various species of animals. Thus the Q^{O_2} value for rabbit articular cartilage has been found to be 0.150 (59), of rabbit fibrous cartilage 0.030 (59), of rat costal cartilage 0.22 to 0.08 (30), and of calf cartilage 0.040 to 0.079 (100, 101). The values for joint cartilage from man and horse are even lower—0.005 (22, 24) to 0.01 (59). It will be noted from these figures that the articular cartilage of rabbits and rats has a greater oxygen uptake than

that of horse and man. The respiration is increased moderately by addition of succinate (101) and, as mentioned above, is markedly stimulated by the presence of methylene blue and to a lesser extent by 2:4-dinitro-o-cresol. The optimal methylene blue concentration for respiratory stimulation has been found to be about 10^{-4} M (59).

The effect of ageing on the respiration of bovine cartilage has been studied in detail by Rosenthal, Bowie and Wagoner (18, 102), who observed a marked decrease in the spontaneous oxygen uptake and a smaller fall in the methylene blue stimulated respiration with advancing years. The results of these important studies have been reproduced in table 3.

The values for the autorespiration were based on observations over a three hour period; the methylene blue stimulated respiration on manometric readings during the first thirty minutes after addition of methylene blue in 2 mgm. per cent concentration.

TABLE 3

The respiration of cartilage tissue slices from cattle of various ages (102)

Age of animal	Number of experiments	Autorespiration		Respiration after addition of methylene blue	
		Q_{O_2}	S.E.	Q_{O_2}	S.E.
Young (under 6 months)	6	0 097	0 006	0 292	0 011
Adult (1–7 years)	11	0 026	0 003	0 224	0 006
Old (8–11 years)	10	0 008	0 0016	0 185	0 009

It will be seen from the table that the spontaneous respiration of cartilage from 8 to 11 year old cattle has decreased to about one-tenth of the value observed in young calves, corresponding to a 90 per cent decrease, whereas the reduction in the dye stimulated respiration constitutes only about 30 per cent. Since the old cartilage continues to show an appreciable response to methylene blue addition, this means that also in the aged cartilage a considerable potential dehydrogenatic capacity is present, and this observation makes it improbable, as also pointed out by Rosenthal, Bowie and Wagoner (101), that failure of this component of the tissue respiratory system is the cause of the reduced oxygen uptake by ageing cartilage. On the basis of Rosenthal's findings it seems much more likely that the decline in respiratory activity with age must be ascribed to a reduction in the function of the oxygen activating component of the metabolic pathway. As shown by Rosenthal, Bowie and Wagoner (100) in concomitant histological studies of old cartilage, the decline in respiration coincides with the appearance of circumscribed regressive anatomical changes in the aged tissue.

In contrast to the rather extensive studies by Rosenthal's group on methylene blue stimulation of the oxygen uptake of old cartilage is the isolated observation by Hills (59) on the effect of dinitro-o-cresol on the Q^{O_2} value of eroded cartilage from a horse. Thus in Hill's studies addition of dinitro-o-cresol caused no increase in cartilage respiration under these circumstances in spite of the fact that this compound, when added to cartilage preparations from younger animals, produced a 3 to 5 fold increase in the oxygen consumption.

The investigations on the glycolytic ability of cartilage date back to 1928 when Hoffmann, Lehmann and Wertheimer (60) were able to demonstrate a notable glycolysis by costal cartilage of dogs. These results were confirmed in 1932 by Kuwabara (75) for cartilage from calves, rabbits and chickens using the manometric method of Warburg. Quantitative determinations of the rate of glycolysis of cartilage from various sources were performed by Bywaters (24), Dickens and Weil-Malherbe (30) and by

TABLE 4

The effect of age on the anaerobic glycolysis of cattle cartilage (102)

Age of animal	Number of experiments	$Q_g^{n_2}$	S E
Young (under 6 months)	11	1.100	0.03
Adult (1–7 years)	13	0.437	0.024
Old (8–11 years)	12	0 259	0.017

Rosenthal, Bowie and Wagoner (100). The results show $Q_g^{n_2}$ values for rabbit articular cartilage of 1.0 (23), for horse cartilage of 0.10 to 0.17 (24), and for bovine joint cartilage of 1.1 (102). For rat costal cartilage the higher values of 1.4 and 1.9 have been noted (30).

The effect of ageing on the anaerobic glycolysis of the cartilage of cattle has been studied by Rosenthal, Bowie and Wagoner (102). The results are presented in table 4 and show a considerable decline in the $Q_g^{n_2}$ values with advancing age.

The Aortic Wall

Structure and measurements

The intima of the aorta in the young human adult has a thickness of about 0.13 mm. (49, 81). It consists of a single layer of endothelial cells lying on a sparse layer of connective tissue and the internal elastic lamina.

The tunica media (49, 81) consists of 50 to 65 concentric elastic membranes 2.5 μ thick, separated by interspaces 6 to 18 μ wide. In the spaces between the elastic membranes are thin layers of connective tissue with collagenous and elastic fibers and smooth muscle cells; between these

structures is found an appreciable amount of basophilic amorphous ground substance. The total thickness of the aortic media in the young adult is 1.30 mm.

The thickness of the aortic wall increases with advancing age. The intima in older individuals may contain several layers of endothelium, and an increased amount of subendothelial connective tissue is often found (123). The media likewise tends to increase in thickness in middle-aged and old individuals. This is well shown in a recent study by Wellman and Edwards (121) on 304 samples of the thoracic aorta obtained from individuals between 20 and 89 years of age. From the measurements of these samples the mean thickness of the media was found to increase from 1.30 mm. to 1.63 mm., this latter value being reached already in the 40 to 49 year age group. A corresponding increase in the thickness of the aortic wall with advancing age has previously been observed in cattle and in the horse by Gerritsen (45) and by Keuenhof and Kohl (63).

Supply routes

As mentioned in the introduction, the internal half or two-thirds of the human aortic media may for practical purposes be considered an avascularized tissue. Both the arterial and venous vasa vasorum from the adventitia in young individuals normally extend only to the junction of the external and middle third of the media (49, 93, 107, 122) at which location a network of anastomizing capillaries is formed. Into this network are received the few vasa vasorum arising from the intimal surface of the aorta; these arterioles, 20 to 30 μ in diameter, usually penetrate the luminal two-thirds of the media obliquely without giving off any side branches.

The aortic media of old individuals frequently possesses the same regional delimitation of the capillary blood supply as obtains in younger adults; in some cases, however, the blood capillaries in old aortas may be seen to penetrate to the internal part of the media and even as far as to the intimal coat (49, 119, 122).

The normal absence of blood capillaries from the internal half to two-thirds of the human aorta can be demonstrated not only through injection experiments but also through analyses of the blood content of homogenates prepared from this section of the aortic wall. If such homogenates are analyzed for hemoglobin by the gasometric method of Van Slyke and Neill (115), a zero reading will be found (68, 69). By employing a sensitive benzidine method to the assay of blood in the human media, the present authors (66) have found the blood content to range between 0.01 and 0.1 per cent. As a consequence of this nearly complete absence of blood from the media of the luminal part of the aortic wall, homogenates prepared of the tissue will appear milk- or cream-colored (figure 1).

The question of how the internal half to two-thirds of the aortic media receives its oxygen supply and supply of nutrients—from the vasa vasorum, the lumen of the vessel or from both of these sources—is a very important one, but a question which in spite of the extensive observations and speculations to which it has been subjected during the last hundred years must as yet be considered as unsolved. A thorough review of the literature concerning this problem was given in 1936 by Ramsey (95).

In the considerations of the importance of the two supply routes for the intramural vascular nutrition, observations based on disease manifestations



Homogenate of the media from a human aorta. The milk-colored appearance of the preparation indicates the nearly complete absence of blood from this section of the vessel wall.

have provided valuable information. Experience has further been gained from an experimental pathological approach, but studies of this latter type are as yet rather few.

Of the investigations supporting the contention of a nutritional supply from the lumen of the vessel the observations by Brüning (21) would seem to carry considerable weight. Brüning examined histologically arteries from a patient who six months previously had been subjected to periarterial sympathectomy with concomitant stripping of the adventitia and in these vessels found the media and the intima well preserved. These findings to Brüning constituted good evidence that nourishment of these layers also under normal conditions takes place from the lumen. As pointed out by Brüning, however, this conclusion may not necessarily be extended to

arteries in which the intima is the site of atherosclerotic changes, since under such conditions the nourishment from the lumen may not be adequate. To what extent these observations may be applied to the question of the nutrition of the much thicker aortic wall is not known. In support of the assumption of a nutritional supply taking place from the lumen of the arteries are further the observations by Anitschkow (5) of in vivo absorption of bile pigments by the intima in jaundiced individuals.

The supporters of the predominant significance of a nutrition from the vasa vasorum are more numerous and include many outstanding pathologists who have been impressed by the occurrence of intimal damage apparently secondary to lesions of the vasa vasorum and indirectly by the fact that the integrity of the arterial wall may persist for long periods after the obstruction of the vessel lumen with a blood clot (76). In this connection should be mentioned the interesting observation by Robertson (97) that senile changes in the human thoracic aorta occur with particular frequency in those regions which are most poorly supplied with vasa vasorum or in other words where the nutrition is supposed to be least adequate. The finding by Lansing, Alex and Rosenthal (77) and Blumenthal, Lansing and Wheeler (17) that changes in the media often precede the development of arteriosclerosis in more luminal parts of the artery would also tend to emphasize the vasa vasorum as the main supply route of the vessel wall.

Of the studies on this subject pertaining to the field of experimental pathology the investigations by Schlichter (106) are of particular interest. Thus Schlichter showed that destruction of the vasa vasorum of the ascending aorta in the dog through coagulation of the adventitia with a cautery was followed by necrosis of the outer and middle thirds of the media, and in other experiments (108) it was demonstrated that such interference with the blood flow in the adventitia when followed by high cholesterol feeding led to arteriosclerotic intimal changes in the areas corresponding to the damaged vasa vasorum.

The conception finally that the blood vessel wall is normally supplied with oxygen and nutrients both from the lumen of the artery and from the vasa vasorum finds its strongest proponent in Petroff (91) who sets the midzone of the arterial wall as the borderline between the areas of the wall predominantly nourished from within and from without. As a basis for this assumption Petroff offers experiments in which a trypan blue solution was injected intravenously into rats and rabbits. Examinations of the aorta at suitable intervals after the injection showed blue staining of the outer and the inner layers of the media, while the middle third of the media remained unstained. The colored reproduction in figure 2 on plate 4 in Petroff's publication, which shows the microscopical appearance

of a rat aorta from a trypan blue injected animal, would seem to support the contention of a double nutritional supply of the aortic wall in a convincing manner.

Although the question of the relative significance of the two possible supply routes for the arterial wall is as yet unsettled, the great majority of investigators seem to be agreed on the importance of interference with the nutrition of the vessel wall for the development of pathological changes in the artery.

Enzyme systems and arterial metabolism

The enzyme systems of the arterial wall have not as yet been the subject of comprehensive studies. It would, however, appear from the recent investigations by Briggs, Chernick and Chaikoff (19) on the metabolism of the rat thoracic aorta that this tissue possesses the necessary enzymes for the breakdown and utilization of carbohydrates. Thus, since the respiration of the rat aorta was found to be inhibited by fluoride addition, it was concluded that phosphorylated intermediates are involved in the metabolism. The oxidative response of the rat aorta to pyruvate and to some members of the tricarboxylic acid cycle also provided evidence that carbohydrates can be metabolized by the arterial tissue.

Evidence for the existence in the rat aortic wall of enzymes capable of synthesizing fatty acids and phospholipids has further been provided in the last few years. Thus it was shown by Chernick, Srere and Chaikoff (27) in in vitro experiments that acetate labelled with C_{14} could be converted to fatty acids by slices of the rat thoracic aorta, not less than 0.4 to 0.7 per cent of the acetate being converted to fatty acids in a two hour period under the conditions of the experiment.

Similar studies (27) using inorganic phosphate labelled with P_{32} showed an incorporation of about 0.8 per cent of the added phosphate into phospholipids per gram of arterial tissue in the course of two hours. This figure is also quite appreciable when it is considered that the phospholipid synthesis by rat liver slices under the same conditions amounts to 5 per cent per gram of tissue, or a synthesis which is only about 6 times higher.

The presence in the human aortic wall and in the wall of the aorta from cattle of a specific ATP-pyrophosphatase with a pH optimum at 9.4 was demonstrated in 1949 by Baló, Banga and Josepovits (11), and in the same year Kirk and Prætorius (67, 68) reported the presence in the human aorta of a monophosphatase capable of splitting disodium phenyl phosphate and disodium p-nitrophenylphosphate. The pH optimum for this latter phosphatase was found to be 5.7 and it was further observed that the phosphatase could be inhibited by fluoride addition.

Phosphatases with a pH optimum in the range of 5.5 to 6.0 have also been reported present in other tissues. The main interest in the finding of the aortic phosphatase lies in the importance which this observation may have in the general discussion of the mechanism of arterial calcification. Since previous investigators had failed to find a phosphatase in the arterial wall—and these negative results can be explained by the fact that earlier studies had been performed only at an alkaline pH—it has generally been contended that calcification of the arteries could not be brought about by a mechanism analogous to that which is believed to be operating in calcification of bone tissue. Whether the aortic phosphatase has any significance for the calcification of the artery is so far unknown, but the presence of the enzyme in the aortic wall will have to be considered in future discussions on arterial calcification.

The present authors (66) have recently been successful in demonstrating the existence of carbonic anhydrase in the media of the human aorta. Experiments with tissue homogenates were conducted both with the boat technique of Brinkman, Margaria and Roughton (20) and with the colorimetric method of Trethewie and Day (113). By both procedures the carbonic anhydrase activity observed was considerably higher than that which could be accounted for by the traces of blood present in the tissue. In all the experiments the concentration of blood in the aortic media samples and the carbonic anhydrase activity of blood from the same individual were determined and the enzyme values for the media corrected for the traces of blood present. It could be calculated that the carbonic anhydrase activity of arterial tissue was about 1/200 to 1/600 of that of a similar weight of red blood cells. As would be expected the carbonic anhydrase in the aortic media was found to be inhibited by addition of sulfonamide.

Concerning the importance of this enzyme for the aortic tissue metabolism the same considerations would seem to apply as outlined in the discussion on the carbonic anhydrase in the lens.

The respiratory metabolism of arterial tissue has been studied by Lazovskaya (78) in 1943 and by Briggs, Chernick and Chaikoff (19) in 1949. In both these investigations aortic tissue from rats was used. As will be seen from table 5, in which the results are listed, the findings in the American and Russian studies show only partial agreement.

In Lazovskaya's investigations homogenates of the aorta were prepared in phosphate buffer solution and the respiration measured by the direct Warburg method at ten minute intervals for one hour, during which period the oxygen uptake was found to remain constant. By this technique a Q^{O_2} value of 2.7 was observed for aortic tissue from young rats of about 3 weeks' age. In a group of 1 year old rats the oxygen consumption of the arterial tissue was found to be much lower, only about one-fourteenth of that of the young rats, with a Q^{O_2} value of only 0.2.

Following addition of succinate to the homogenates a notable rise in the respiration was observed, namely an increase from 2.7 to 4.0 in the samples from the young animals and from 0.2 to 0.6 in the preparations from the old rats. Approximately the same Q^{O_2} values were noted when, besides succinate, cytochrome c was added to the flask content. These latter values give a measure of the capacity of the succinic dehydrogenase system of the tissue. Since after the addition of succinate and cytochrome c the Q^{O_2} values of the aortic tissue from old rats still were much lower than the oxygen uptake in the homogenates from the young rats, it was concluded by Lazovskaya that a marked decrease in the succinic dehydrogenase capacity takes place with ageing of the arterial tissue.

In the studies by Briggs and his associates on the respiration of rat

TABLE 5

Respiration of rat aortic tissue (19, 78)

	Young rats Q^{O_2}	Old rats Q^{O_2}
Lazovskaya, 1943		
Spontaneous respiration, homogenate.	2.7	0.2
Addition of succinate, homogenate	4.6	0.6
Addition of succinate and cytochrome c, homogenate	4.0	0.8
Briggs, Chernick and Chaikoff, 1949		
Spontaneous respiration, homogenate	0.0	0.0
Spontaneous respiration, tissue slices	1.1	1.1
Addition of succinate, tissue slices	2.6	2.3

aortic tissue both the homogenate and the tissue slice techniques were used. As it will be seen from the table, Briggs, in contrast to Lazovskaya, failed to observe a definite oxygen consumption by tissue homogenates, whereas with the use of tissue slices Q^{O_2} values of about 1.0 were noted. This figure is about one-tenth of that found for rat liver slices. It is possible that the difference between the oxygen uptake of homogenates in Lazovskaya's and in Briggs' experiments is due to differences in the homogenization technique used.

A further discrepancy between the American and the Russian observations on rat aortic tissue is the finding of practically the same Q^{O_2} values for young and old arterial tissue in Briggs' experiments as contrasted with the marked difference between young and old animals noted by Lazovskaya. Both the American and Russian investigators are, however, in agreement on one point, namely with regard to the effect of succinate addition. As seen from table 5 such addition in Briggs' experiments also was followed by a marked increase in the Q^{O_2} value. This response to succinate, in

combination with the observation by Briggs that addition of malonate produced an inhibition of the oxygen uptake, indicate, as did also Lazovskaya's result, that succinic dehydrogenase participates in the metabolic process. A definite but smaller increase was also noted by Briggs after addition of lactate, pyruvate, alpha-ketoglutarate, citrate and acetate, whereas glucose, glycine and alanine were without noticeable effect on the Q^{O_2} values.

In reviewing the interesting findings by Lazovskaya and by Briggs it should, however, be noted that so far no observations have been reported on human arterial tissue and that, in the experiments on animal tissue, studies on the anaerobic metabolism of the arterial tissue, on the rate of glycolysis, are lacking.

The studies by Briggs and his associates on the oxygen uptake of rat aortic tissue were extended to include measurements on aortic tissue from rats which had been fed thyroid for ten days before the animals were sacrificed and determinations on tissue from another group of animals which had been treated with propylthiouracil for a thirty day period. It is of considerable interest that the aortas from the thyroid treated rats showed a 25 per cent increase in oxygen consumption as compared with the untreated animals, whereas the propylthiouracil treated group showed Q^{O_2} values 20 per cent lower than normal.

Although the experimental data on the metabolism of arterial tissue so far reported are rather few, the observations by Briggs on the effect of thyroid and propylthiouracil on the oxygen uptake of rat aortic tissue and the findings by Chernick and associates (27) of an ability of the rat aorta to synthesize both fatty acids and phospholipids suggest that a further knowledge of the normal and abnormal arterial tissue metabolism might contribute to the understanding of the factors responsible for the development of arteriosclerosis. It seems not unlikely that an extension of the tissue metabolism studies to human arteries would yield results of value, and such in vitro investigations performed on normal and pathological blood vessel samples might constitute still another significant approach to the study of human arterial disease.

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29

AGEING OF THE SKIN

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The skin so definitely mirrors the changes wrought by time and exposure to the rigors of this world that its appearance has become a yardstick by which layman and physician alike estimate the age of an individual. Everyone knows that young skin is rosy, smooth and elastic, while old skin is pale or yellowed, wrinkled and flaccid. The hair is an appendage of the skin, and the silvery hair of age or the loss of hair plays its part in delineating the picture of the old man.

A number of factors probably play a role in determining the rate at which age changes take place in the skin. One of the principal ones is heredity. Although no specific investigations correlating heredity with ageing of the skin can be cited, it is a common observation that the members of some families become gray-haired at an earlier age than do those of other families, and that in some family lines, the individuals keep the ruddy complexion of youth until well past middle-age. There is at least one congenital disease of the skin, xeroderma pigmentosum, which emphasizes the relation of heredity to those changes in the skin which we usually associate with senescence. In individuals afflicted with this disease the skin shows, even in childhood, the mottled pigmentation, foci of atrophy, keratotic areas and telangiectases that are commonly found in senile skin. Macklin (1, 2), in a study of 198 families in which some members of each group were affected, has shown that xeroderma pigmentosum is an inherited disease due to recessive determiners. Thus in this disease, we have evidence that some of the characteristics associated with ageing of the skin can be hereditarily transmitted.

In patients with xeroderma pigmentosum exposure to sunlight seems to exacerbate the disease. In normal persons, too, whose occupations cause them to be subjected to sunlight for long periods, the skin of the

exposed portions of the body will show senile changes in early middle life or before. Dermatologists, who are aware of the role of light in the production of these senile changes, often speak of this prematurely aged skin as "farmers' and sailors' skin". Both in patients with xeroderma pigmentosum and in individuals excessively exposed to light, the occurrence of malignant change in the skin is quite common. The incidence of skin cancer increases with chronological age and this environmental factor of exposure to light seems to play a role in the development both of senile change and of malignancy.

In addition to hereditary and certain environmental factors which affect the rate of development of age changes in the skin, endocrine disturbances also may be related to this process. Most of the experimental support for this hypothesis is based on studies in which the topical application of estrogens or androgens to the skin of old persons resulted in a reversion of the senile changes. The atrophic epidermis increased in thickness; the collagen fibers became less fragmented and more nearly approached the "wavy character" of the collagen bundles in young skin; and the elastic fibers became more numerous and showed less degeneration (3–5). In certain endocrine disturbances, the skin prematurely ages. For example, in hypophysial dwarfism and the related disease progeria, in which the hypophysis is destroyed or severely damaged by a tumor, the skin of individuals who are chronologically young resembles that of old age. It is dry, flabby and often wrinkled. In Simmond's disease, which usually occurs in multiparous women, and is caused by destruction of the anterior lobe of the pituitary, the skin is also affected. It is pale and wrinkled and the subcutaneous fat is scant. Therefore, at least two lines of evidences indicate that the endocrines may play a role in producing the changes in the skin that are associated with ageing; first, the rejuvenation of old skin by the topical application of endocrines, and second, the precipitation of age changes in the skin in individuals with certain endocrine diseases.

In addition to these hereditary, environmental and endocrine factors, many others may play a part in the ageing process, but their nature and interrelationships are not yet clearly understood.

Morphological Changes

Epidermis

From the standpoint of morphology, a considerable amount of information is available concerning the structure of the skin at different ages. As skin grows old the epidermis becomes more and more atrophic, and alterations in what has been called the pattern of the rete occur. The interdigitations of the epidermis with the dermis which are usually called rete pegs are not really pegs or finger-like projections of the epidermis into

the dermis. The structure of the proximal surface of the epidermis in young adults is that of a honeycomb or net, and the so-called rete pegs are the lateral walls of each small unit of the net. This pattern of the rete

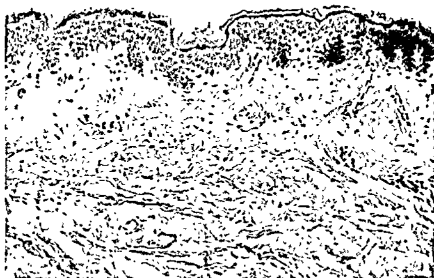
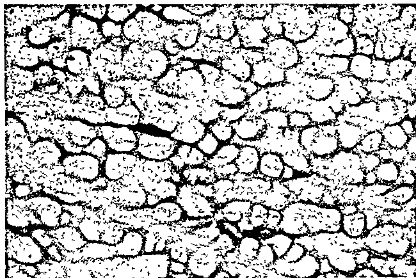
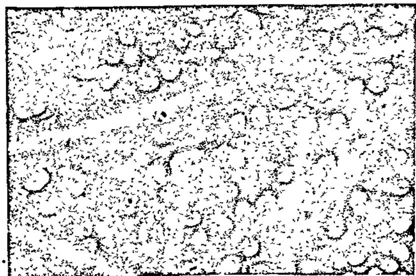




FIG. 1. Sections of human [illegible]

is altered with age (6) so that in old individuals the net-like structure is completely lost and the epidermis becomes a thin flat sheet (figs. 1 and 2). Creases or wrinkles of microscopic dimension begin to occur in the epi-





[illegible] epidermis from the thigh which show changes

dermis in the third and fourth decades, and in them the first evidence of atrophy appears. Later this change is evident over wider areas until in extreme old age the entire epidermis is atrophic.

The quantitative studies of Evans, Cowdry and Neilson (7) help to define what is implied in the rather loosely used term, "senile atrophy" of the epidermis. They measured the thickness of the epidermis in fourteen male subjects; seven young, varying in age from 19 to 30 years, and seven old who were 80 to 94 years of age. They measured areas between the rete ridges where errors of measurement due to the angle of cutting could be avoided. The skin examined was from the antecubital region. The epidermis of the seven young skins was thicker than the old by an average of 6.5 micra. They believe that this variation in thickness of the epidermis in young and old skin may be explained by differences in the properties of the dermis which cause greater shrinkage in young specimens, and lead to "crowding" of the epidermal cells. In other words, these investigators believe that the young epidermis appears thicker in sections because there is more shrinkage of the underlying tissue after the skin has been excised. They conclude that except for the marked difference in reaction of the connective tissue beds young and old epidermis would show very little difference in thickness. Since the microscopic appearance of senile skin resembles rather closely that of certain diseases of the skin in which atrophy of the epidermis is known to occur and can be seen grossly it is difficult to believe that this explanation accounts for the whole picture.

Regional differences may complicate the picture of the process of ageing in the epidermis. Ejiri (8) counted the number of layers of epidermal cells in young and old cadavers. In his material, with advancing age, the number of layers diminished on the head and face and increased on the dorsal surfaces of the arm, hand and foot. In other words, from his observations the epidermis of the face seems to undergo atrophy in old age while that of the extremities does not. Further work is needed to better define the regional variations that may occur during the process of ageing.

Studies of age changes in the various layers making up the epidermis have not given entirely consistent results. In a study of the normal skin of twenty individuals varying in age from the newborn infant to 78 years Hill and Montgomery (9) found no changes in the stratum corneum on parts of the body covered by clothing; some suggestion that the granular layer may increase in thickness with age; and no relationship between age and the increase or decrease in the number of cells in the prickle-cell layer. They found that moderate atrophy of the rete ridges occurs in old age on both exposed and unexposed skin. Evans, Cowdry and Neilson (7), on the other hand, found that the stratum corneum and the granular layer seem to become thinner in old skin. However, they examined only one region,

the cubital fossa. Ejiri (8) found no change in the granular layer with age. Changes in the stratum corneum and stratum granulosum may be of considerable importance. For example, these layers do not take part in the erythema response of the skin to sunlight, but variations in their thickness might alter the site of maximum erythema reaction in the deeper layers of the skin and lead to abnormal changes there. In other words, they may act as filters for external factors that influence the skin.

There is often a spotty increase in pigment in the basal layer in old epidermis. This can be seen grossly as hyperpigmented areas on the face and backs of the hands in many older individuals. Two studies shed some light on the problem of pigment distribution, that of Hill and Montgomery (9) who examined by conventional staining methods human skin from areas of the body which are protected by clothing, and that of Ejiri (8) who examined skin from unprotected areas. Hill and Montgomery found that no increase in pigmentation occurred on unexposed parts of the body, but Ejiri did find an increase on exposed areas. This would seem to indicate that exposure to light and other environmental agents may play a role in producing this change.

Thuringer and Cooper (10) found an increase in the number of mitotic figures in the epidermis in older individuals. Their study was carried out on specimens of human normal abdominal skin which were removed at surgery and fixed immediately. They recorded the number of mitotic figures encountered per 100,000 epidermal cells in each of 37 specimens of skin removed from individuals varying in age from 1 month to 77 years. There was a consistent increase in the number of mitotic figures present with advancing age. This is rather hard to correlate with the usually accepted idea of lowered metabolism in the older individual, but is interesting in view of the fact that benign hyperplastic lesions such as keratoses and carcinoma occur more frequently in senile skin.

Dermis

COLLAGEN AND ELASTIC FIBERS. There is evidence to support the idea that both the collagen and elastic fibers of the dermis undergo change with age. Degenerative changes frequently become apparent in the fourth decade of life and may appear even earlier in persons who have been exposed continuously to the elements. The dermis on exposed parts of the body stains differently in older individuals than in young. Unna (11) pointed out long ago that the fibers of the sub-papillary layer have a basophilic

also affected in these areas. They are often swollen and fragmented and

they, too, are slightly basophilic. Unna called this modified elastic tissue elacin. Sometimes the altered collagen and elastic fibers seem to merge together to form a more or less homogeneous mass and he called this altered fibrillar material collacin. He thought it represented a fusion of collagen and elacin (fig. 3).

The results of detailed histological studies of the changes in the collagen and elastic fibers of the dermis with age have varied considerably. Strobel (12) studied specimens of unexposed skin taken from the umbilical region,



FIG 3 Skin of the cheek of a 74 year old man. (Verhoeff's elastic tissue stain). The elastic tissue fibers in the upper part of the dermis show clumping and degeneration.

the internal aspect of the thigh and the upper arm of 240 individuals belonging to all age groups. These people had not had any disease of the skin, and had died as the result of an accident or from some acute infectious disease. He found that the principal age change was in the collagen fibers. From the middle thirties on these fibers showed increasing atrophy, rarefaction and parallelization and later degeneration into collacin. Strobel does not believe that the elastic fibers show any degenerative change with age but only extension in length and parallelization which he interprets as the effect of overstretching.

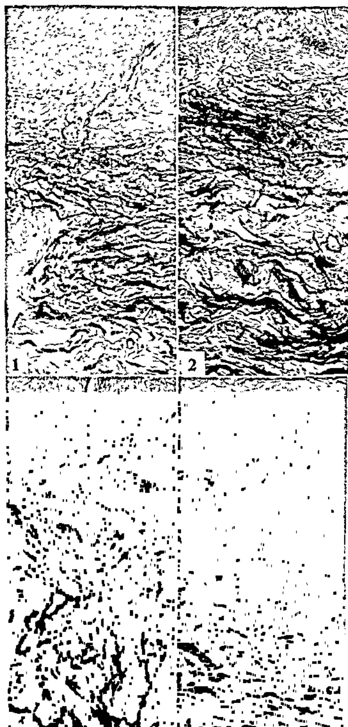
Hill and Montgomery (9), on the other hand, found only very minimal changes in either the collagen or elastic fibers in specimens of human skin taken at necropsy from 20 individuals varying in age from a newborn infant

to 78 years. The skin which they studied was from unexposed areas of the body (webs between the toes, pubis, axilla, chest and scalp).

Ejiri (8, 13, 14), studying 718 specimens removed at necropsy from exposed areas (forehead, chin, cheeks, bridge of nose, eyelids, parotid region back of the hand and forearm) found definite changes in the elastic tissue and minimal changes in the collagen. The elastic fibers showed degeneration and fragmentation with advancing age. Vitreous changes in the fibers appeared after the age of 40. Degenerative changes in the elastic fibers of the middle part of the dermis began in the fourth decade and became distinct before the fifth decade. Such changes in the lower part of the dermis usually began at the end of the sixth decade and were distinct in persons above the age of 60. These changes were more pronounced in men than in women. Ejiri observed degenerative changes in the collagen fibers in the papillary layer, but they varied from region to region, both as to degree and age of onset. He concluded that the senile changes occurred principally in the elastic fibers and not in the collagen.

Two other recent studies on age changes in elastic tissue are worthy of mention, that of Dick (15) and that of Ma and Cowdry (16). Dick obtained specimens of skin from 32 individuals whose ages ranged from infancy to over 65 years. The anatomical sites studied were the sole and dorsum of the foot, the medial and lateral surfaces of the leg, thigh, forearm and upper arm, abdomen and chest. In individuals over 65 years of age changes in the elastic tissue were quite apparent. In the deeper elastic tissue layer the fibers showed rough thickening, irregular fragmentation of the ends and variability in length. In contrast to the even distribution of elastic fibers in young individuals, condensation and aggregation of the fibers occurred in the old. In the subepidermal plexus of fine elastic fibers, the fibers were thicker in old than in young subjects and occasionally they were completely absent. Dick did not report any observations on the collagen fibers.

Ma and Cowdry (16) studied the dermal elastic tissue in biopsy specimens obtained from a group of 11 young male adults who ranged in age from 19 to 32 years and from a group of 8 senile males whose age varied from 78 to 94 years. The tissue that they studied was removed from the antecubital region of living patients. Marked differences were observed in the two groups. In the older group a decrease in elastic tissue was quite evident (fig. 4). In the subepidermal plexus this change was more apparent than in the deep fiber layer. In the subepidermal plexus a splitting of elastic fibers into component fibrils was observed in the senile skin. These workers did not find in their specimens the vitreous, or hyaline, degeneration observed by Ejiri, and even transverse fragmentation was rare. They, too, did not study the collagen fibers.


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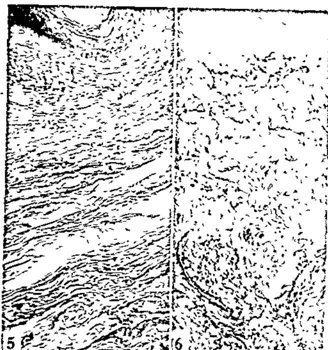


Fig. 4. All figures are photomicrographs [illegible]

It seems apparent from these studies that the elastic tissue of the dermis undergoes definite change with age. Ejiri, who was studying skin from exposed areas, seems to have observed the most pronounced degenerative changes. That changes in all the components of the skin would be more intense on exposed areas would be expected from the gross appearance of the skin in older individuals in many of whom the skin of the trunk is less wrinkled and flaccid than that of the face or hands. Both Dick and Ma and Cowdry noted a decrease in elastic tissue in old age. Some difference of opinion exists as to whether the collagen or the elastic tissue is responsible for the gross physical property of the elasticity of the skin. However, whether the elastic fibers can stretch and thus directly condition the extensibility of the skin, or whether they are rigid and by their [illegible]

skin of older individuals.

These studies do not clearly define the nature of the changes in the

collagen with age and some investigators have failed to demonstrate any change. As *Hill* and Montgomery point out it is not possible on a purely morphologic basis to offer any definite proof of the merging of collagen and elastic fibers which Unna postulated and Ejiri's studies cast some doubt on whether such a merging takes place.

All the studies which have been discussed were done on paraffin sections stained by conventional methods. Of recent years, the work of Gross and Schmitt (17) and of Gross (18, 19), in which the electron microscope was used to examine the finer structure of collagen and elastic fibers, opens up attractive possibilities of investigating the changes in the structure of the fibers that occur with age. Gross and Schmitt have already studied samples of human abdominal skin obtained at autopsy from 16 individuals varying in age from 1 hour to 89 years. The collagen fibril which can be seen with the ordinary light microscope is composed of many ultra-microscopic fibrils. On examination with the electron microscope each of these fibrils displays a periodically banded pattern with six intraperiod bands. This intrinsic structure of the fibril is the same in infant and adult skin. The average width of the fibril is about 1000 Å in adult skin; fibrils from infant skin show widths as small as 300 Å, although the average width is not significantly different from that of adult skin. The fibrils are surrounded by a gelatinous amorphous material. The greatest quantity of this material was found in infant skin where, at times, it almost completely obscured the axial periods of the collagen fibrils. Work on the structure of elastic tissue has been started, and the elastic fiber has been shown to be a "two component system composed of bundles of trypsin-resistant threads of characteristic form and size, plus a trypsin-sensitive, heat-resistant amorphous binding matrix". Studies such as these are fundamental and give promise of shedding light on the nature of the degenerative changes in the dermis which accompany advancing age.

The newer histochemical methods may also furnish a different approach to this problem, but, as yet, no extensive studies have been published.

Ground Substance and Permeability. The fibrillar elements of the dermis are surrounded by an amorphous, probably gelatinous material, which is known as the ground substance. Ma and Cowdry (16) as a side-observation in their study of ageing of the elastic tissue of human skin, noted a change in this important substance with age. In sections of skin, which were 25 micra in thickness and were stained with orcein, "a cloudiness or lack of clarity" was apparent in the ground substance about the elastic fibers in old skin which was not present in young. These investigators were using biopsy material from living subjects which was *promptly* and uniformly fixed. Earlier studies by other workers were made largely on autopsy material, and this may explain why this difference in the

ground substance has not been noted before. Ma and Cowdry believe that their observations indicate that there is an increase or a change in the properties of a material, or materials, in the ground substance of senile skin. They point out that if this substance is the basophilic polysaccharide, hyaluronic acid, or a related substance, the permeability of senile dermis would be expected to be somewhat less than that of the dermis of young individuals.

Duran-Reynals (20), reviewing work done on animal skin, stated that the skin of old animals is less permeable than that of young ones. However, in human skin permeability is dependent on several factors. Strauss and Necheles (21) showed that human skin of old individuals was more permeable than that of young. They injected the dye, Evan's blue, intracutaneously in the forearm of 137 subjects who ranged in age from 12 months to 90 years. The resulting wheal or dye stain was smaller in the younger age groups, and the dye remained visible in the injected area after 24 to 48 hours in a significantly larger number of younger subjects. Both the lymph supply and the structure of the dermis are probably factors which play a role in these results. Using vital dyes, Levin, Silvers, and Berkowitz (22) have shown that the looser the skin, the greater the lymphatic spread of an injected dye. Since the skin usually becomes looser with advancing age, the lymphatic spread also becomes greater. This looseness of the skin is associated with looseness of the subcutaneous areolar and elastic tissue, and loss of subcutaneous fat, changes which become more pronounced in old age.

The only conclusions that can be drawn from these observations is that, morphologically, age differences exist in the appearance of the ground substance, and that there are also age differences in permeability of the skin. The morphological and physiologic observations have not been completely correlated as yet and cannot be until more is known about chemical, cellular and physical differences in young and old skin.

Blood Supply of the Dermis. The dermis has a rich vascular network. Two large arteriolar plexuses are present: one in the deeper portion of the dermis and one in the mid-dermis from which numerous small branches arise and run as terminal arterioles toward the epidermis. Even in persons who do not have hypertension, some change in the blood vessels of the skin with age would be expected in connection with the changes in the fibrous elements of the dermis. To establish a base line for their study of the arterioles of the skin in essential hypertension, Farber, Hines, Montgomery, and Craig (23) established the wall-to-lumen ratio of cutaneous arterioles in normal persons of different ages. Their measurements were made on microscopic sections of pieces of skin obtained from the upper arm, lumbar region and calf of 52 persons who had normal blood pressure

and whose ages varied from 10 to 89 years. Table 1 presents their results. Apparently, even in persons whose blood pressure is normal, there tends to be an increase in thickness of vessel walls with age. It may be possible to correlate this morphological evidence of changes in the vascular bed with age with some physiological difference in the skin at different ages.

Popoff (24) found that the number of glomic units in the dermis decreases in old age. The glomus is a highly organized arterio-venous anastomosis which has, in addition to its vascular component, a rich nerve supply. These structures are most numerous on the ventral surface of the hand and foot, but may be found elsewhere on the body surface. In persons over 60 years of age the number of glomic units per square centimeter begins to decrease and this decrease progresses with advancing age. The glomus is thought to be concerned with temperature regulation and conservation of body heat. The decrease in number and atrophy of these structures in old age is interesting in view of the fact that many old persons complain constantly of a sense of chilliness.

TABLE I

Age of normal individuals and mean ratio of thickness of wall to diameter of lumen of arterioles

After Farber, Hines, Montgomery and Craig—modified slightly

Age	Number of persons	Mean wall to lumen ratio
years		
10-19	1	1:2 27
20-29	7	1:2.17
30-39	9	1:2.08
40-49	15	1:2.18
50-59	14	1:2.22
60-69	3	1:1.87
70-79	2	1:1.95
80-89	1	1:2.01

Skin Appendages

HAIR. *Changes in the hair that occur during the life span of the individual* are so obvious that everyone is aware of them, although some false impressions concerning these changes are generally accepted. For example, many people think that in white adults the head hair becomes coarser as the individual grows older until old age is reached, when the hair again acquires a degree of fineness equal to that of early childhood. Careful measurements by Wynkoop (25) and Trotter (26) have failed to substantiate this impression. The diameter of the shaft of scalp hair increases during

childhood, but until the age of 10 to 15 years it remains less than that of adult hair. Wynkoop (25) has shown by measurement of 483 samples from 82 individuals, varying in age from 3 hours to 91 years, that after childhood is past, the hair-shaft diameter of scalp hairs bears little or no relationship to the age of the individual. Trotter (26) confirmed these findings. She has pointed out, however, that the hair of different regions of the body shows a definite relationship, specific for the region, between the size of the hair and the age of the individual. She has shown that hairs of the leg gradually increase in diameter throughout life (27); that hairs of the axillary and pubic regions increase appreciably in size before 20 years and remain relatively constant thereafter (27), and that hairs of the beard region, in both sexes, show the greatest increase in diameter between 20 and 30 years and remain constant in subsequent decades (28).

Graying of the hair due to loss of pigment is quite definitely associated with advancing age, but Trotter (26) has shown that the color of hair which has not lost its pigment also changes with age. The hair of young individuals is lighter in color than that of older ones and the incidence of darker tones increases with age. For example, the blonde hair of youth tends to become light brown in middle age. In most individuals whitening of the hair accompanies advancing age, but it may also be a symptom of certain physiological disorders, such as those that occur in some of the endocrine diseases. Morphologically, in white hair there is an absence of pigment in and around the cells of the cortex, but the cause of this change in pigment formation and distribution is still not understood. Gray hairs have been said to have a greater diameter, that is, to be coarser, than pigmented hair in the same individual. Trotter (26) measured samples of hair from 51 individuals who were becoming gray, and in only 31 per cent of the cases did the gray hairs exceed in caliber their pigmented neighbors.

Baldness is also often associated with advancing age, but there are so many types of alopecia which bear no relationship to age that any discussion of this phase of the problem in the present state of our knowledge seems futile.

Sebaceous Glands and Sweat Glands. The statement is found in the literature (29, 30) that sebaceous and sudoriporous glands are atrophic and diminished in number in senile skin, but experimental work to prove this point seems to be lacking. Way (31) and others have observed hyperplasia of the sebaceous glands in the region of the forehead in middle-aged and old individuals, but this is probably not constant for all individuals. Way (31) also makes the statement that sebaceous glands are active through middle age, and that after that they begin to atrophy.

With regard to the apocrine sweat glands Way and Memmesheimer (32) claim that these glands are not reduced in old age in either number or

size. No concrete information is available concerning age changes in the eccrine sweat glands.

Chemical Changes

Work on the chemistry of normal skin is far less extensive than that on morphology, and attempts to correlate what is known about chemical changes with age are very few. Most of the studies that have been done have been on mineral content of the skin.

Brown (33) did such a study on human skin. He used samples obtained at necropsy, some from fetuses and newborn infants, and from individuals ranging in age up to 82 years. The whole skin was used for his determinations after it was freed from hair and subcutaneous tissue by scraping with a knife. Determinations were made for moisture and total ash content and for the amounts of calcium, magnesium, sodium, potassium and silicon present in the skin. The moisture content was variable and did not correlate with age. The total ash content declined from birth through the first decade of life and then rose steadily in individuals who were from 10 to 80 years of age. The curves for calcium and magnesium parallel rather closely that for the total ash content. They show a decrease in these minerals early in childhood and then a consistent increase throughout the rest of the life span. Although the determinations of sodium and potassium were not so clear-cut, they tend to follow this same pattern. The silicon content of the skin decreases with age.

MacCardle, Engman and Engman (34, 35) in their investigation of mineral changes in neurodermatitis by the method of micro-incineration and spectrographical analysis, used skin from 83 normal persons as controls so that their results give some information on age changes although this was not the primary purpose of their work. The individuals from whom skin was taken varied in age from infancy to 91 years. Most of the biopsies examined were obtained from the cubital fossa or popliteal space, but some specimens from the neck, back, abdomen, head and face, foot, hand and chest were included in this series. One-half of each biopsy was studied using the micro-incineration technique, and the other half was subjected to spectrographic analysis. By the latter method spectrograms were made which recorded line densities for calcium, copper, magnesium, iron, phosphorous and zinc. By use of the micro-incineration method the minerals in the tissue are seen in the same topographic relationship that exists in fixed tissue, and the distribution of these elements is perhaps closely comparable to that obtaining in living tissue. The results of these studies showed that the ash content of normal skin fluctuates between hypermineralization and hypomineralization in children until about the age of 10 years, when a definite change toward hypermineralization begins. The mineral content increases slowly and consistently from childhood to old

age. "The primary mineral change in old age appears to be a shift of calcium and magnesium from the deeper part of the epidermis to the corneum and to the dermis." The results of this work agree rather well with those of Brown who used routine chemical methods for his determinations.

Suntzeff and Carruthers (36) have studied the mineral composition of isolated epidermis. Using the method of dry heat (50°C) described by Baumberger, Cowdry and Suntzeff (37), they separated the epidermis cleanly from the dermis in sufficient quantities to make chemical determinations of potassium, sodium, magnesium, and calcium on it. They obtained their material from human extremities or breasts which had been surgically amputated and in which the skin was not involved by disease. The skin studied came from 18 individuals who varied in age from 15 to 79 years They were not able to demonstrate correlation of mineral content with age. These results are interesting when compared with those of Brown. Apparently, the slow rise in mineral content with age, which Brown showed in whole skin, must actually occur in the dermis, since Suntzeff and Carruthers were not able to show any change in the epidermis with increasing age. The shift in calcium and magnesium from the epidermis to dermis which MacCardle, Engman and Engman demonstrated by the method of micro-incineration must involve amounts that are too small to be detected by chemical methods.

Some work has been done on the sulfur content of the skin with reference to age changes. Sulfur in the skin exists essentially in organic combination and a large part of it is probably in the form of cystine and cysteine. Other known sulfhydryl compounds in the skin are glutathione and methionine. Klauder and Brown (38) determined the total sulfur content of human skin from infancy to old age (0–76 years) and of rabbit skin from birth to maturity. The sulfur content of the skin decreases with age in both species. The normal percentage of sulfur in the skin of human infants ranges from 0.4 to 0.5 per cent; it decreases in the first few years of life to about 0.35 per cent; at adolescence it is about 0.30 per cent and in adults of all ages it ranges from 0.25 to 0.30 per cent. This decline in sulfur content from birth to adolescence, when it reaches a plateau and remains quite constant throughout adult life, is in accordance with the known importance of the sulfhydryl compounds as growth factors. For example, cystine is indispensable for normal growth and development.

Physiological Changes

Only a few studies on physiological changes in the skin correlated with age have been done. They are on diverse phases of the problem, and most of them have not been repeated by more than one observer. Kirk (39) has recently studied human skin lipid secretion with reference to age, and has carefully reviewed the literature on the subject. He collected the skin se-

cretions from a 10 square centimeter area of the forehead from 234 individuals who varied in age from 19 to 102 years. Of these, 116 were white men and 94 were white women, who were over 40 years of age. Two collections were made on each subject; one after the secretion products had been allowed to accumulate for twelve hours, and a second after another four hours had been allowed to elapse. In this way, the rate of secretion could be determined, as well as the total amount for a twelve hour period. Sex differences were found in this study. Approximately the same twelve hour sebaceous secretion was noted in both men and women until the age of 70. During the eighth decade the mean twelve hour secretion in women was only one-half as great as that observed in men, and in the ninth decade, it was only one-third as great. The secretion showed a moderate tendency to increase with old age in the men. The rate of secretion was more constant from youth to old age in men, whereas the secretion in young women was four times as great as in old women. It would seem from this study based on but one area, that the sebaceous glands do not undergo atrophy in old age in men. The findings in women are less clear-cut.

In a parallel study by Kvorning and Kirk (40) an attempt was made to correlate Kirk's findings with regard to lipid secretion with the gross appearance of the skin. Observations were made on the thickness, turgor, moistness and degree of wrinkling of the skin and on the size of the skin "pores". Thickness was judged by folding the skin between the observer's fingers and grading it into one of three groups: thin, normal or thickened. In the men there was no correlation between thickness of the skin and amount of secretion, whereas in the women those with thicker skin had higher secretion values. Turgor was estimated by observing the skin resilience subsequent to lifting the skin into a fold. Turgor was reduced in most of the individuals examined, and in the men the secretion values were the same whether turgor was normal or reduced. In the women those with normal skin turgor had higher secretion values. No correlation could be demonstrated between secretion values and either moistness or degree of wrinkling of the skin. The "skin pores" were classified into four categories: not visible, visible, distinct and enlarged. In both sexes, those individuals with distinct or enlarged "pores" showed high levels of lipid secretion. Apparently not too great a correlation exists between the amount of lipid secretion and the gross appearance of the skin.

A study of water loss from the surfaces of the finger tips and toe tips of senile subjects has been made by Burch, Cohn and Neumann (41). The method used consists of passing dry oxygen through chambers covering the skin of fingers and toes, and then conducting the moisture-laden oxygen through cold coils. The amount of the water loss is measured by the difference in weight of the coils before and after the passage of oxygen. The results give a quantitative measure of the rate of sweating. As controls for

their study of patients with hypertension, Burch, Cohn and Neumann made measurements on thirteen normal subjects whose ages ranged from 8 to 44 years, and on eight essentially normal senile subjects, whose ages varied from 70 to 85 years. The older individuals showed no signs of renal or cardiac failure. In the older group the rate of sweating was definitely less rapid than in the younger. Moreover, the rates from one observation period to another were much less variable in the senile group. The reduced rate of sweating in the old may be one of the manifestations of reduced physiologic activity which occurs with age. This study sheds no light on the mechanism which produces the reduced rate of sweating. It may be caused by a decrease in the number of sweat glands, by partial atrophy, or by decreased function, or by all three factors.

Another physiologic problem that has received some attention is that of variability in oxygen consumption of the skin with age. Adams (42) has demonstrated a decline in the oxygen consumption of rat skin with increasing age and Fardon, Brotzge and Loeffler (43) have shown similar variations in mouse skin. Walter and Amersbach (44) have shown that human skin also shows a decline in the respiratory rate. Specimens of skin were obtained from the lateral chest wall below the axilla from 31 healthy white women who varied in age from 20 to 65 years. The respiratory quotients (cubic millimeters of oxygen consumed per milligrams of dry tissue per hour) were determined by means of a microrespirometer and this data was correlated with the age of the subjects. The respiratory rate of the skin of the older women was lower than that of the young. This study provides another measure of the lowered metabolism that accompanies the ageing process.

Elasticity is a physical property of the skin which varies with age. In several recent studies attempts have been made to definitely measure the extent of the change in this property. The Schade elastometer is an instrument which has been used to measure the elastic properties of the superficial tissues. It registers the degree of indentation immediately following the application of a standard weight (50 grams) to the skin surface; the total indentation after the weight has been in place for several minutes; the immediate rebound following removal of the weight; and the total rebound several minutes after the weight has been removed. The immediate indentation, the immediate rebound and the total rebound are expressed in percentages of the total indentation. In this way comparative data can be collected on the behavior of the skin to localized pressure and on its resiliency. Kirk and Kvorning (45) made such measurements on the skin over the tibia of 24 young individuals between the ages of 18 and 25 years and of 28 old individuals between the ages of 60 and 86 years. Pronounced differences in the two groups were observed. The indentation following the application of the weight to the skin was greater in young than in old

individuals and the immediate rebound of the tissue subsequent to the removal of the weight was also greater in the young than in the old. The data collected in these experiments give physiological evidence of the decrease in elasticity of the skin with age. In a similar experiment Chieffi (46) has tested the elasticity of the skin in old individuals after topically applying steroids to the skin. Localized massage of the skin of old women with estrogen in oil resulted in an improvement in the elastic properties of the skin; but parenteral estrogen produced no change. The elasticity of the skin of old men was not improved by either topical or parenteral administration of androgens. This work is of interest in view of the histologic observations of M. A. Goldzieher (3) Eller and Eller (4) and J. W. Goldzieher (5) on senile skin which had been treated with estrogens. As has been mentioned previously, they were able to demonstrate a reversion of the microscopic picture of senile skin toward that of young skin following local application of steroids.

Dick (47) has studied elasticity of the skin by a somewhat different method. He has devised an instrument which will record the expansion of a disk of excised skin when it is exposed to pressure. With this instrument he has studied skin, removed at necropsy, from 17 individuals who varied in age from 15 to over 65 years. For each individual, skin was tested from several anatomic sites (epigastrium, medial and lateral sides of the thigh and medial and lateral sides of the leg). The skin from young subjects expanded much more gradually for initial increases of pressure than did skin from old subjects. The skin in old people is lax and when it is subjected to pressure there is an initial pronounced expansion for small increases in pressure. The limit of skin expansion was reached at much lower pressures in old skin than in young. Dick believes that the fragmentation and irregular distribution of the elastic fibers of the dermis in old age, which he has discussed in a previous paper (15), are responsible for the initially greater expansibility of old skin.

These two studies have a slightly different approach to the problem of the change in elasticity of the skin with age but both show that senile skin is less resilient than young skin.

Pathological Changes

A number of pathological changes are associated with advancing age. In addition, the skin of old persons reacts differently to disease than does that of the young. For example, old skin does not react as violently to irritation as does young. As Epstein (30) has pointed out, the very acute picture of a contact dermatitis, such as is seen in young people, is rarely encountered in the aged. However, even a subacute minor dermatitis is slower to heal in old individuals.

SENILE PRURITUS. Severe itching of the skin is a common disturbance found in old individuals. It often has a generalized distribution although usually the trunk is chiefly involved. This disease is ascribed to atrophic and degenerative changes in the skin, but the mechanism by which the sensation of itching is produced is not clearly understood.

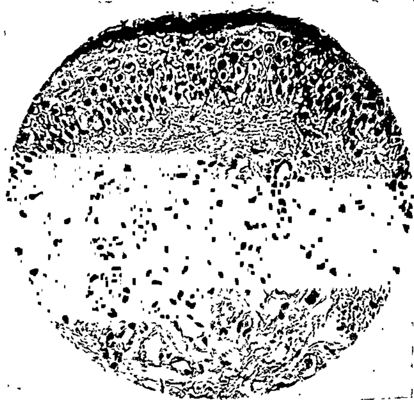
SENILE ELASTOSIS. Changes in the fibrous components of the dermis are thought to be responsible for a clinical picture seen in many old persons to which Weidman (48) has given the name senile elastosis. The skin becomes yellow in color, opaque, and leathery in consistency and deep, thick furrows and wrinkles form. When the subcutaneous fat is lost, the skin can easily be raised from the underlying structures or depends from them in folds. The changes are more conspicuous on exposed areas of the body. Microscopically, the elastic tissue shows not only degenerative changes, but is increased in amount. Changes are thought to occur in the collagen bundles also. In some cases, Weidman (48) has observed infiltration of the degenerated elastic fibers with fine lipid droplets and he believes that the fatty changes are responsible for the yellow color observed grossly. Senile elastosis apparently represents only an exaggerated form of the senile changes that normally occur in ageing skin.

ACROCHORDON. Another abnormality of the skin that appears in older individuals is acrochordon or "cutaneous tags". These are small soft pedunculated growths which are usually only one to two millimeters in diameter. They occur on the neck and thorax especially in middle-aged women and vary in number from a few to hundreds. Templeton (49) found that microscopically these lesions are small papillomas covered with intact, slightly thickened epidermis. The fibers of the dermis have a loose, spongy, areolar arrangement and the blood vessels and lymph spaces are dilated. The elastic tissue fibers are thinned and diminished in number. The lesions seem to represent a local hyperplasia of fibrous tissue. The etiology of these lesions is unknown, but there is some indication that their development may be associated with some endocrine imbalance since they are more common in post-menopausal women. Similar lesions are said to occur in pregnant women and regress after delivery. Although these lesions are much more common in women, Templeton mentions the occurrence of these defects in two old men.

SENILE ECTASIA. These lesions which involve the superficial blood vessels of the skin are quite commonly found in old skin (fig. 5). They are slightly raised, red lesions, a few millimeters in diameter, which occur on the trunk in older people. They are usually multiple. Microscopically, the lesion consists of a small circumscribed group of dilated capillaries in the upper part of the dermis. Gans (50) advanced the idea that senile degeneration of the connective tissue is responsible for the development of these lesions.

SEBORRHEIC KERATOSIS (VERRUCA SENILIS). In the epidermis, also, some lesions occur which are definitely more common in old individuals than in young. The keratoses, both the seborrheic keratosis and the senile, are examples.

The seborrheic keratosis is a sharply circumscribed, round or oval, raised,



edition.)

roughened yellowish brown to brownish black lesion that occurs most frequently on the trunk. It is found much more commonly in elderly individuals than in younger people and the lesions may be single or multiple. The name is misleading since the lesions bear no relation to sebaceous glands. On microscopic examination, the epidermis shows a pronounced elevated thickening. Included within it are numerous cysts filled with laminated keratin and islands of connective tissue which represent the tips of distorted dermal papillae. Some lesions contain a great deal of melanin

pigment. The underlying dermis is essentially normal. The lesions grow slowly, but may become one to several centimeters in diameter. They are usually benign. In fact, it is debatable whether they ever become malignant.

SENILE KERATOSIS (KERATOMA SENILIS). The senile keratosis is also a lesion which arises in the epidermis of older individuals. These lesions are usually only moderately elevated, irregular in outline and grayish in color. They are surmounted by an adherent thin scale. As opposed to the seborrheic keratosis, the senile keratosis is found more commonly on exposed areas of the skin such as the face, backs of the hands and forearms. These lesions, which are frequently multiple, develop in skin which shows either

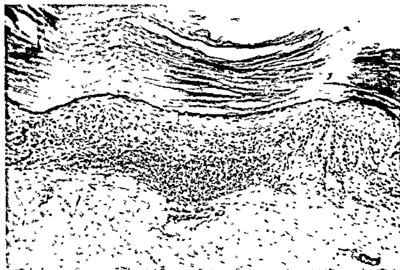


FIG. 6. Senile keratosis from the dorsum of the hand of a 66 year old man

gross or microscopic evidence of senile degeneration. They are usually considered to be "pre-cancerous" lesions, since if they are left untreated, squamous cell carcinoma will develop in 20 to 25 per cent of the cases. Microscopically, the senile keratosis shows hyperplasia of the epidermis with a variable amount of dyskeratotic change (fig. 6). Cowdry and Andrews (51) have recently published a cytologic and cytochemical study of such lesions.

CARCINOMA. Cancer of the skin is definitely more common in older individuals and is probably the most serious disease to which senile skin is particularly susceptible. Schrek and Gates (52) analyzed the data obtained from one group of 581 patients who had cutaneous carcinoma and found that at time of onset the median age of individuals with basal cell carcinoma was 57.3 years and that of individuals with squamous cell car-

cinoma was 66.2 years. They found an even higher age of onset in another group of 495 patients in which the median age at time of onset for persons with epidermoid carcinoma was 69.8 years, and for those with basal cell carcinoma, 61.5 years. Since cancer of the skin can be readily observed and biopsies taken with ease, it is usually diagnosed early and accurately, and treated effectively. The cure rate is very high.

With regard to the high incidence in older people of epidermal "precancerous" lesions, like the senile keratosis, and carcinoma, two facts are of interest. First, senile epidermis normally tends to become atrophic, and yet, these pathologic lesions of epidermal origin show hyperplasia. Secondly, Thuringer and Cooper (10) have found a high mitotic index in senile epidermis in spite of the fact that it is atrophic. Is there some correlation between these two facts? It is interesting to speculate that when the senile epidermis is stimulated by some carcinogenic agent, known (such as actinic rays) or unknown, this old skin, with its relatively high rate of cell division, has better potentialities for increased hyperplasia than does young skin.

Lentigo Senilis. Another attribute of aged epidermis is its increased ability to produce pigment. This pigment is splotchily distributed in the form of smooth, brown irregular areas, measuring from a few millimeters to a centimeter or more in diameter, on the dorsa of the hands, forearms and face. These pigmented macules seldom appear before the fourth or fifth decade and slowly increase in size and number thereafter. Such lesions occur in approximately 25 to 30 per cent of persons who are more than 50 years of age. They are asymptomatic and bear no relationship to the general health of the patient. Cawley and Curtis (53) have recently studied these lesions histologically and have found that they resemble lentigines. The basal layer of the epidermis is heavily pigmented and numerous clear cells are present. From many of the rete pegs eccentric thumb-like buds project which are made up of strongly dopa positive cells. These lesions are distinguished from freckles by the age of onset and depth of color, and by the fact that sunlight does not influence their development. They differ from ordinary lentigines in size, localized distribution and age of onset. They do not become malignant.

Pigmented Nevi. Although pigmented nevi do not increase in number, with age, Lund and Stobbe (54) have made a detailed study of 200 pigmented nevi which were excised from patients varying in age from 0 to more than 60 years of age. They found that a correlation exists between the histologic appearance of the nevus and the age of the patient. "Judged from the transitions noted in the different age groups, nevus cells appear to differentiate slowly from foci of clear cells found in the epidermis and follicles and along the sweat glands. Further differentiation principally in adult life, leads to the formation of fusiform cells with fibrils which in

many instances resemble neurofibrils and tactile corpuscles." This is the first study of a large group of nevi excised at different ages. It is of great interest from the standpoint of ageing since it shows that even lesions, which have been thought to be congenital malformations in the skin do not remain stable throughout life, but undergo changes with age.

The importance to the dermal pathologist of an accurate knowledge of age changes in the normal skin is self-evident. Without such information, the microscopic picture in disease may be misinterpreted. Lund and Stobbe's study indicates that some pathological lesions may also change in aspect with age. This adds another factor which must be taken into account in evaluating some pathological entities.

Summary

Age changes in the skin are so readily observable that everyone is aware of them. The way in which they are produced is not so clearly understood. Several factors undoubtedly play a role in their development, and the most obvious of these are heredity, environmental conditions, such as long-continued exposure to sunlight and inclement weather, and endocrine imbalances.

Morphologic changes in the skin that occur with advancing age have been rather carefully described by many observers. In brief, these changes are atrophy of the epidermis; focal areas of increased pigmentation in the epidermis; degenerative changes in collagenous and elastic fibers of the dermis; increase in thickness of the walls of the blood vessels; graying of the hair; and possibly atrophy of the sebaceous glands and sweat glands. The changes in the connective tissue fibers of the dermis are certainly an important factor in the ageing process, but the nature of these changes is not clearly understood. Conventional staining methods on histologic sections are not sufficiently sensitive to resolve this problem. The newer histochemical methods and electron microscope studies give some promise of shedding new light on this perplexing subject. Age changes in the ground substance of the dermis have not been adequately studied as yet, although there are some indications that such changes do occur.

Studies on the chemical changes in the skin with age have been few. Those that have been done, are for the most part concerned with mineral content. The total ash content, as well as the quantity of many of the individual minerals such as calcium, magnesium, sodium and potassium, seems to decrease from birth through the first decade of life and then to rise steadily throughout all the subsequent decades. Much more work could and should be done on the chemistry involved in age changes in the skin.

There is also very little known about the physiologic changes in the

skin that are correlated with age. Some studies have been done on variations in the lipid secretion, water loss, oxygen consumption, elasticity and permeability of the skin. In many of these experiments rather crude methods have been used. Only one or two studies have been done on each phase of the subject, so that the results stand on the observations of one investigator or one group of investigators. This field presents a challenge to the gerontologist.

Many diseases and cutaneous abnormalities to which senile skin is especially susceptible have been described. The pathogenesis of most of these disorders, however, is still but poorly understood. Skin cancer which shows a definite increased incidence in old individuals, is probably the most serious disorder to which senile skin is particularly susceptible. Because the lesions can be observed readily, they are usually diagnosed and treated early. Consequently, the number of cures is very high.

The recent work of Lund and Stobbe (54) on benign nevi is of interest from the standpoint of pathology because it shows that not only do the normal constituents of the skin change with increasing years, but a congenital abnormality of the skin, the pigmented nevus, also undergoes changes with age. This study is thought-provoking. How many other lesions of the skin might show changes in their "natural history", as Lund and Stobbe call it, with age?

Perhaps because of the very obviousness of age changes in the skin, their detailed study has been somewhat neglected, and great gaps still remain in our knowledge. This is a fruitful field for further investigation.

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SKELETON

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Introduction

Bones have three functions. They serve 1) as structural supports and agents in locomotion, 2) as a reservoir of mineral, particularly calcium, for use in blood coagulability, muscle tone, kidney function and activity of the central nervous system, and 3) as housing for the hempoietic tissues of the red marrow. Age changes are manifest throughout the life span in respect to each of these, but in each case differentiation between ageing and infirmity is often difficult. Adequately comprehensive data have not accumulated and final interpretations are not possible.

The major part of existing information is descriptive of the morphological changes in the skeleton from birth to advanced years. Variations in these phenomena and in their association with time have been incompletely studied.

Current criteria of ageing in the preadult and the adult skeleton contrast in four important particulars, exclusive of preadult growth changes.

1. Data on the changes from birth to the early part of the third decade are from subjects of definitely known age and condition, while knowledge of changes over the remainder of the life span has been derived essentially from subjects of identified sex and stock whose ages, condition and provenience can generally be presumptively, but rarely positively known.

2. Preadult subjects in reported series have been principally from economically secure social strata and thus reflect a better nurture than the destitute whose skeletons have provided the series for adult standards.

3. The roentgen-ray has been the means of identification and measurement of age characters in the preadult skeleton, while the ageing features described for the adult skeleton refer to the naked bones and are not satisfactorily or consistently identifiable by means of the x-ray in the

living subject. Yet in orthopedic and other clinical conditions in which age assessment would be of practical value, the condition of the skeleton can be studied only through the roentgenogram.

4. In the preadult skeleton, sex, constitutional type, endocrine balance and nutritional condition have been found to influence significantly the expression of ageing, but very little is known of the influence of these factors on the adult skeleton.

The material upon which current adult criteria are based thus embodies more uncertainties than that of preadult standards. Appraisement and interpretation of age change in the adult skeleton must also take into account *the effects of the processes used in the preparation of the skeleton*, for no process, from natural desiccation to steam maceration, is without its effects on the bones. These effects tend to be heightened by long storage. Appearances of bone surface possibly attributable to age may actually be the result of preparation procedures.

Clearly, important desiderata for future studies will be the development of adequate techniques for appraisal of skeletal age in the living adult and the determination of the degree to which standards based on cadaver populations are applicable to the general population and/or particular samples of the latter.

General Considerations

Although present concern is principally with age changes in the latter portion of the life span, after dimensional growth has ceased, one of the chief features of these changes, their irregularity, cannot be properly appreciated except in the perspective of the changes over the whole life span.

All of the gross changes now identified with ageing process show an orderliness or patterning. In fetal life when the primary centers of ossification appear, the vertebral column may serve as an example. Here the centers for the bodies appear first in the lower thoracic region and spread up and down the column, while those for the laminae appear first in the cervical region and gradually progress down the column. In the appearance of secondary or epiphysial centers of ossification during the first four years of life, this phenomenon of patterning shows itself in the appearance of these centers in sheaves and in a definite order (22). It is notable in late adolescence in the age order of epiphysial union and the tendency for the epiphyses to unite in groups (72–75).

The vividness of the protracted pattern of differentiation on the symphysial surface of the pubic bone has made this area one of the principal age determinators in the adult skeleton.

Both pattern and bursts of activity are evident in the order and degree

of suture closure, which extends over nearly the whole of the adult life span.

While preadult as well as adult indicia of age exhibit much variation, the coordinated picture for the entire skeleton presents less uniformity in adult than in preadult periods. Controlled differentiation might be said to be characteristic of preadult ageing. In contrast, progressive loss of control of differentiation, of the even advance of change in the several parts of the skeleton, is distinctive of adult ageing

For simile, this progressive loss of control of differentiation might be likened to a parade in which West Point cadets, veterans of World War II, veterans of World War I and veterans of the Spanish-American War were marching, in that order. The presumptive formation and cadence would be the same for all, but we should notice that the West Pointers alone would be holding their lines across the ranks and down the files. Each successive group of veterans would show progressively less ability to maintain the form and the pace, until the Spanish War soldiers would show little evidence of formation and make little pretense of keeping in step. The very irregularity of the oldest group, however, would constitute a kind of aggregate uniformity which makes the similarity of senescents comparable with that of infants.

The skeleton, like other parts of the body, is responsive to those influences, endocrine, nutritional, genetic and otherwise, which produce variations in the evidence of physiologic time as registered against chronologic time.

Acceleration of physiologic ageing in comparison with chronologic age is most dramatically apparent in the condition of progeria, in which a child of six may have rapidly progressed to and show tissue characteristics of a man of sixty.

On the other hand, there are many conditions associated with disorders involving the sex glands and thyroid in which development is more or less arrested, so that characters of youthful period are retained in advanced adulthood.

The complexities and endocrine relationships of these conditions are not yet explained, but there is evidence that development of maturity is under pituitary control, while dimensional growth and arrest of maturation may be ascribed to thyroid influence.

Materials for Study of Skeletal Ageing

The current standards of skeletal ageing stem largely from the vision and labors of one investigator, Dr. T. Wingate Todd, the late and deeply lamented author of this chapter in previous editions of this volume. Ade-

quate historical treatment of earlier studies of the anatomical criteria used may be found in Todd's own papers and in reviews such as that by Ashley-Montagu (6). Todd's perspective upon the problem encompassed all its aspects and in the laboratory and collections which he built, studies were initiated and brought to various stages of completion which enhanced our knowledge of nearly all the multilateral aspects of the problem.

During a twenty-seven year period at Western Reserve University, Todd assembled, between the years 1912 and 1939, a collection of 2600 documented skeletons of known sex and stock and a death certificate age, from anatomical laboratory cadavera. A second great collection of 1500 similarly documented skeletons, initiated somewhat later and assembled over a shorter period of time, was gathered at Washington University in St. Louis by Dr. Robert J. Terry. These two collections, comprising 4100 individuals, mostly whites and American Negroes of both sexes, are unique in the world both for size and documentation (17). There are not now in process of assemblage any collections of similar magnitude or known origin. Consequently, the combined Reserve and Washington collections constitute the main body of skeletal material available for study of the ageing process in the adult as determined by observations upon actual skeletons in statistical quantity. This material is the best available and there is no prospect of better.

The Reserve collection

Since the Reserve collection is the one upon which most of the ageing studies thus far reported have been based, a brief description of the population sample it represents will be in order.

A comprehensive analysis of the death certificate data on this collection was made in 1932 (16–19). At that time 2139 individuals were included, of whom 82 per cent were males and 18 per cent females. Two-thirds of the males and slightly more than half of the females were whites; the remainder were American Negroes, with occasional Chinese, Mexicans and Indians.

A birthplace was stated for 1177 or 55.6 per cent of the individuals. Of these 723 were whites, 52.6 per cent of that group, and 453, Negroes, 61.1 per cent of the latter. Internal evidence indicated that the picture presented by the sample of stated birthplace held true for the entire lot.

Sixty per cent of the whites were of European birth, but only six individuals, or 1 per cent, of the Negroes were foreign born. The regional concentration of the birthplaces among twenty-five European countries indicated representation of the population movements known as the "old" and the "new" immigrations. The native born whites were principally of foreign parentage, an origin learned in part from specific statement

and in part deduced from the states in which they were born (14), principally Ohio, New York, and Pennsylvania, their names and their lineaments.

The Negro cadavera came from 27 states and in representative number from a different and much wider territory than the native whites. A heavy majority were born in Georgia, Alabama, and South Carolina, with many from Tennessee, Virginia, Kentucky, Mississippi, North Carolina and Arkansas. Most of these Negroes had come north in the industrial migrations which began during World War I.

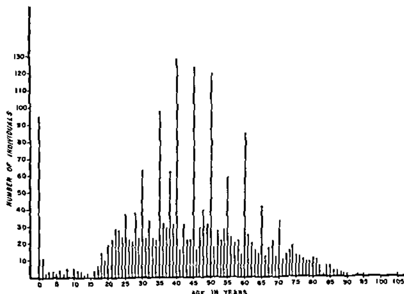


FIG. 1. Distribution by age in years of 2116 cadavera in Western Reserve University collection.

The mortality curve of the cadaver population plotted from the stated ages exhibits a peak in middle age. The median age of the collection is 45 years. The separate curves for the component groups provide illuminating comparisons (fig. 1). The "old" immigrants (median age 58 years) present a distinctly old age curve; the "new" immigrants (median age 42 years) a middle age curve; and the Negroes (median age 37 years) a still younger curve.

Immigrants as a class are composed of the active age groups, containing few children and old people. When the age curves of the several groups of the laboratory population are considered in the light of the uniformly low economic level represented and the period during which the collection analyzed was assembled (1911–31), it will be seen that the skeletal collection

embodies evidence of three mass movements and the great economic depression which began in 1929.

Roughly about two hundred years ago a great colonization and national development program attracted settlers of the "old" immigration who came from the British Isles, Germany and the Scandinavian countries. Since this immigration reached its peak in about 1880, thirty years before the collection was started, cadavera of this stock would be expected to show the oldest curve, as they do.

With the beginning of the new era of accelerated industrial progress toward the close of the last century, huge numbers of "new" immigrants from eastern, central and southern Europe were called to this country to supply the unskilled divisions of labor. This movement was abruptly terminated by World War I and later permanently restricted by law. The "new" immigration reached its peak and sudden termination soon after the Reserve collection was begun, but as many of these people had come over in the two preceding decades, most of the "new" immigrants among the cadavera approximate middle age.

To fill the demands for crude labor created by the war and the reduced European supply, the Negro swarmed northward. The Negro migration occurred in the midst of the years of collection, so that the truest reflection of all would be anticipated in this group. Records of duration of residence in Cleveland showed that many of the first arrivals among the Negroes terminated in the anatomical catacombs. The unusually early age peak of the Negro curve represents environmental decimation at its height. Since there were few aged among the migrants and the survivors had not had time to grow old, there is no old age component in the Negro curve. The mortality curves of both "old" and "new" immigrant groups might have been expected to have shown similar form at appropriately earlier times.

Enumeration of the causes of death in this cadaver population revealed that the diseases of poverty and exposure—tuberculosis, pneumonia, and external causes—produced more casualties than in the general population. Particularly was this true for the Negro cadavera among whom respiratory diseases took the same precedence as in national Negro mortality at that time.

There was a close similarity between the Reserve cadaver population and Pearl's population of persons necropsied at Johns Hopkins (52, 53), in respect to the age distribution by race and sex, and their general populations. This similarity naturally follows the common social origin of the material.

It has been necessary to set forth in this detail the demographic picture of the Reserve collection not only to provide a necessary picture of the

nature of the material, but to correct the unfortunately common impression that data from the death certificates of individuals without funds for burial are of little value. In the aggregate these data embodied so much truth that it was possible to show from them many reflections of the history of the city in which the cadavera were recruited. A considerable portion of this truth resides in the stated ages of the cadavera.

Status of Age Appraisal Technique

In the initiation of ageing studies upon this collection, the difficulties of the material dictated the methods employed. The absence of birth certificate ages for the cadavera could not be compensated, therefore, Todd emphasized repeatedly that the approach was first to determine the pattern of ageing differentiation in the several parts of the skeleton and

TABLE 1

Number of individuals used in studies of pubic differentiation and suture closure and number in present Cleveland and St. Louis collections

Sex and stock	Pubic differentiation	Suture closure	Western Reserve	Washington University
Male white	306	307	1474	574
Male Negro	90	120	733	580
Female white	47	58	211	106
Female Negro	22	29	225	257
Total	465	514	2643	1517

then to associate this pattern with time. The studies of specific criteria, such as pubic differentiation and suture closure, were made during the course of assembly of the collection and of necessity were based upon less than half the material eventually available (table 1). Moreover, and again of necessity, the studies relating to one feature did not report upon the condition of the others in the same skeleton. Todd gradually developed for his own use a technique for age assessment in the adult skeleton which he demonstrated to a few others, but had not perfected for publication, prior to his untimely death.

Various workers from time to time have used the published studies on pubic differentiation and suture closure, reinforced with direct or remote acquaintance with Todd's assessment technique, to develop assessment techniques of their own. The confidence of these workers in their results has varied. Some have felt unable to attest the validity of their appraisals with desirable satisfaction, while in other hands the technique has appeared sufficiently reliable to be incorporated in bulletins of the Federal Bureau of Investigation (37–41). The existence of considerable dissatis-

faction with the scientific validity and general utility of current methods of appraising age in the adult skeleton must be freely acknowledged.

It had long seemed apparent to the present writer that a comprehensive study embracing the whole of the Cleveland and St. Louis collections might resolve the current nebulae and permit the preparation of an atlas which would show adequately the march of time as recorded on the skeleton, and differences related to the individual, sex, stock and other significant factors. In 1941 he actually embarked upon such a project and devoted a year and several summers to it. This work served to emphasize the dif-

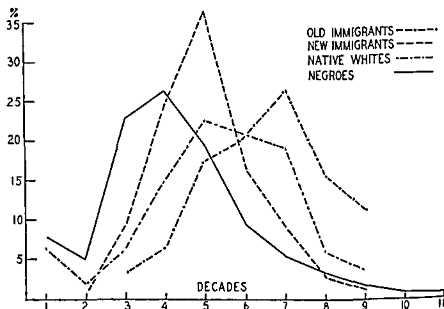


Fig. 2. Percentage distribution of stocks in Western Reserve laboratory population by age in decades

ficulties of the problem as well as the advantages of material in such large statistical quantity. It further demonstrated that sufficiently comprehensive studies of the combined material of both collections can eventually offset in large measure the absence of certified ages on these skeletons. Under present circumstances, however, this will require many investigations, many workers and many years.

The present account will attempt to summarize as simply and clearly as possible, the present status of the problem of age changes in the adult human skeleton, and the import of the various facets of the problem.

Ages of the Reserve Cadavera

It is, of course, unchallenged that significant error is inherent in the death certificate ages of unclaimed deceased consigned to an anatomical

laboratory. These ages may represent a coroner's guess, or, even the subjects' own antemortem estimates. Todd gave serious attention to this subject.

In an early paper (70) he showed that the frequency polygons of the stated ages in the Reserve collection showed peaks in the years which were multiples of five. This was confirmed by Cobb (16) in greater detail when the series had grown much larger (fig. 2). Todd ascribed these peaks to the tendency of people who were either uncertain or unconcerned as to their exact age, to give it in terms of the nearest year which was a multiple of five. This would apply also to coroners or others charged with official responsibility for estimating the age of unknown deceased persons. Todd further showed that this tendency to give the age as the nearest five year lustrum became increasingly conspicuous after age 30. He cited that this was by no means a modern tendency, as it was apparent in Macdonell's (46) mortality curves of ancient Romans.

The lustral peaks of the cadaver mortality curve, therefore, represent both antemortem subjective estimate as well as, in lesser degree, postmortem objective guess.

Adult Skeletal Age Determinators

The humerus is the skeletal criterion for the transitions into adolescence and into adulthood. Its distal epiphysis is first of those of the long bones to unite and its proximal, the last. A united proximal epiphysis establishes the subject as of age 19 or beyond.

Closure of the basilar suture (basisphenoid with basioccipital) has proved a convenient standard (30) for early adulthood (age 20–21) although no specific study of the closure of this suture has been published. The eruption of the third molar may have contributory but not definitive value in this connection. In many populations the third molar frequently may not erupt. In Eskimos unerupted third molars are rarely if ever found after closure of the basilar suture (61).

During the remainder of the third decade the laggard epiphyses, those of the vertebral bodies and sternal end of the clavicle unite. Again, precise studies of the dates of union of these epiphyses have not been reported.

From about age 20 into advanced years the progress of pubic differentiation and suture closure have been described in detail.

Of corroborative value as age advances, but as yet without established norms, are dental wear, the occurrence of lipping on the articular margins of the long bones, ossification of costal cartilages, spondylitis as distinct from arthritis of the vertebral column and changes in the areas adjacent to certain joints, such as the manubrio-gladiolar articulation.

Modifications with time in the vascularity, surface texture and cancel-

lous structure of the scapula, make this bone a valuable auxiliary indicator of age.

Pubic differentiation

Todd's studies of the age changes on the symphysial surface of the pubic bone constitute the most exhaustive investigation of ageing in any skeletal feature of the human adult. The eight papers of this series describe the structural changes, the variations associated with sex, race and individual deviation, the comparative morphology of symphysial change, and appraisement of human pubic differentiation by the x-ray.

The symphysis pubis was chosen for this investigation because it shows "definite sequence of modification strictly associated with age," and because unlike any other skeletal feature, it "tells its tale throughout life, although less clearly from forty years onward than at an earlier age" (63–67, 71).

Todd had envisioned a series of studies to embrace all the adult skeletal features in which age change is readily manifest. Of these projected inquiries only those on the symphysial face of the pubic bone and suture closure were completed.

Todd showed the pubic metamorphosis follows essentially the same pattern in both mammals and man, and he devised a scheme based on comparable anatomical criteria in other regions, for showing the relation of the pubic sequence of change to life period in mammals and man. In addition, he expressed the age relationship in terms of years for man.

Relative to the fact that the ages of his standard skeletons could not be confirmed by birth certificates or other unquestionable evidence, he stated that "the difficulty of getting precise and reliable data regarding age was greatly underestimated at the beginning of our skeletal investigation and this difficulty is responsible in larger degree than any other single circumstance for the long period between the inception of the Western Reserve University collection and the publication of studies thereupon." His careful and comprehensive analysis of the factors involved led to the conclusion that "at present we must adopt the course of accepting the stated age" (Todd (63) p. 292). Obviously, no other course was possible.

Todd divided the pattern of pubic differentiation into ten phases, each of which was associated with an age range. The pattern of change is illustrated by the accompanying figures.

In post-adolescent and early adult life the subepiphysial symphysial face presents a transversely billowed surface with an increasing sharp dorsal margin and bevelled ventral area. Overlying this subepiphysial face is a cartilaginous epiphysis, the ventral part of which alone ossifies. The close textured epiphysial ossification is apparent early in the third decade (fig. 3).

It forms upper and lower extremities and a ventral rampart for the symphysial face with which it may or may not fuse at this time. Under the ventral rampart rarefaction appears in the billowed subepiphysial bone so that the epiphysial rampart may actually form bridges of bone.



Fig. 3 Fig. 4

Fig. 3 Symphysial face, pubic bones. No. 711 W. R. U. Negro, male, aged 22 [illegible]

Dorsal margin and commencing textural transformation in surface are apparent

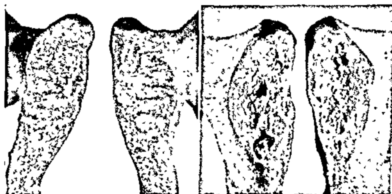


Fig. 5 Fig. 6

Fig. 5 Symphysial face, pubic bones. No 525 W. R. U. Negro, male, aged 22 years. All parts seen in figures 3, 4 are present in this example but are retrogressive in type The cause of variants in ruggedness of expression in different bones is not yet known.

Fig 6 Symphysial face, pubic bones. No. 791 W. R. U. Negro, male, aged 28 years Upper and lower nodules and ventral rampart are now losing themselves in the general textural transformation.

Most frequently however the bony epiphysis, as it ossifies, fuses immediately with the underlying bone so that the billowed surface becomes glazed by close textured new bone (fig. 4). Distinction between epiphysial and underlying bone is often difficult (fig. 5).



Fig. 7



Fig. 8

Fig. 7. Symphysial face, pubic bones. No. 314 W. R. U. White, male, aged 42



Fig. 9. Symphysial face, 1.5 pubic bones. No. 253 W. R. U. White, male, aged 58 years. Marked erosion of surface and breakdown of ventral margin.

In the latter part of the third decade the billowed texture is lost and a typical ovoid symphysial face results, formed dorsally by the pubic bone itself but ventrally, and at upper and lower extremities, by ossified fused epiphysial bone (fig. 6). Early in the fifth decade the symphysial face presents an oval surface of which the texture is relatively smooth, delimited by clearly outlined dorsal and ventral margins meeting at raised upper and lower extremities (fig. 7). Toward the end of the fifth decade a narrow

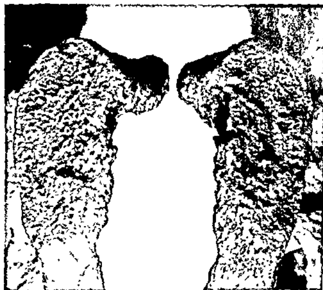


FIG. 10. Symphysial face, 1 5 pubic bones. No 359 W. R. U White, male, aged 63 years. Complete transformation of surface into the irregularly eroded texture of advanced age

beaded rim develops on the margins as in other articular surfaces of the skeleton (fig. 8).

During the sixth decade erosion of surface and breakdown of ventral margin begin to modify the configuration of the symphysial face (fig. 9). In the seventh decade this modification has progressed to the complete transformation of the surface into the irregularly eroded texture of advanced age (fig. 10). This terminal disorderly configuration is a true feature of the ageing process. Although the morphological features are indistinguishable from those of pathological origin it is not due to disease. It illustrates a blend of ageing and infirmity where orderly control of differentiation is lost although the bizarre and often grotesque overgrowth of frankly pathological origin is lacking (63-64).

Suture closure

Four papers by Todd and Lyon on endocranial and on ectocranial closure in white males and Negro males, respectively, constitute the most extensive published studies on human suture closure (79–82). These reports were based exclusively upon the male series because eliminations for irregularities in closure would have reduced prohibitively the already inadequate female series for demonstration of closure pattern and age relationship (table 1).

The method used was the determination of modal progress in closure. Skulls which did not individually show even progress were discarded from the series and treated separately. Forty white and 41 Negro skulls were so rejected. These constituted 13.3 and 34.2 per cent of their respective series. There remained thus 267 male white and 79 male Negro skulls upon which the findings on order and time of closure were based. The small size of this series and the principle of rejecting irregular specimens have undoubtedly been the source of much of the difficulty encountered by others who have attempted to use the condition of the sutures as a basis for age assessment.

Stewart (61) found in 20 Eskimo skulls considerable irregularity and asymmetry in closure of the coronal and sagittal sutures and that the coronal seemed to close before the sagittal, the reverse of the finding of Todd and Lyon in whites and American Negroes. Cattaneo (15), apparently unfamiliar with the more recent studies, concluded from a study of 100 skulls of unspecified origin in Argentina, that sutures were useful only as a suggestive indicator of age in medico-legal cases, because 33 per cent show variations from the rules for closure which he gleaned from early writers (10–11).

Unlike the procedure in the case of the pubic bone, individual specimens were not used by Todd and Lyon to illustrate the progress of suture closure. This was shown by composite graphs which represented the average closure of all the skulls in the series.

The numerical and hence graphic representation of the progress of closure was made possible in the following way. First, the sutures were classified into three regional groups, namely those of the vault (roof of the skull), the circum-meatal (about the ear-hole), and the accessory. The vault sutures are three, the sagittal, coronal and lambdoid. The circum-meatal, arranged around the external auditory meatus, are four, the spheno-temporal, squamous, parieto-mastoid and masto-occipital, and the accessory sutures, intermediate in closure relationships between the other two groups, are two in number, the spheno-parietal and spheno-frontal sutures.

These nine sutures were assigned linear subdivisions of their own, following the terminology of Broca. The respective subdivisions totalled 21 units as shown in table 2.

For each subdivision of each suture the degree of union, referring to the extent of confluence of surface of adjacent bones and not to any deep condition, was indicated by one of the figures 0, 1, 2, 3, or 4, 0 meaning no union and 4, complete union. Thus the condition of each suture may be represented by a formula, as, Sagittal 0143, meaning, pars bregmatica,

TABLE 2

Sutures and subdivisions for which closure is recorded

No	Suture	Subdivisions	Units
		Vault	
1	Sagittal	Bregmatica, vertica, obelica, lambdica	4
2	Coronal	Bregmatica, complicata, pterica	3
3	Lambdoid	Lambdica, media, asterica	3
			10
		Circum-meatal	
4	Speno-temporal	Superior, inferior	2
5	Squamous	Anterior, posterior	2
6	Parieto-mastoid	Taken as a whole	1
7	Masto-occipital	Superior, media, inferior	3
			8
		Accessory	
8	Spheno-parietal	Taken as a whole	1
9	Spheno-frontal	Orbital, temporal	2
			3
Total			21

no union; pars verticis, one fourth united; pars obelica, completely united; and pars lambdica, three fourths united.

From the formula of each suture for all the skulls in the several age groups recorded in this way, graphs were prepared showing the progress of union. The dates of commencement and completion of closure ultimately derived for white and Negro series are presented in table 3, with incidental comments on the course of progress.

The following principal conclusions emerged:

1. Suture closure in general becomes apparent upon both endocranial and ectocranial surfaces of the skull at the same time. Ectocranial closure

and is almost constant on the ectocranial surface where, however, it does not present the characteristic heaped-up feature (79–82).

Closure of sutures between the bones of the face commences in general later than but pursues its course parallel with suture closure in the cranium. No adequate description has so far been given of the age relationship of facial suture closure in man though Schweikher (58) has made a detailed record of the sequence of union between the several facial bones of the hyaena as a type of mammal and Krogman (35–36) has described the same process in anthropoids and Old World apes.

Because considerable confusion still exists in the interpretation of suture closure and because of the procedure of rejecting, for cause, certain skulls in their relatively small series by Todd and Lyon, it seemed that additional light might be obtained if the conditions of the sutures in the skulls of the combined Reserve and Washington collections were tabulated and analyzed. This the present writer has done and it is hoped that the results may shortly be published.

It is to be emphasized that the function of sutures and the significance of their closure has not been adequately clarified. The recent studies of Brash (12) confirmed the Hunterian principle that bones grow and change form by surface accretion and surface absorption. Epicranial deposit and resorption on the endocranial surface would permit the skull to grow without the presence of sutures. The charting of growth of the individual bones of the skull by Todd and his associates in man and in certain mammals has indicated that growth changes in the bones may be observed along the suture lines (85). In addition, the cranial deformities such as scaphocephaly, oxycephaly, acrocephaly, etc., have been traditionally ascribed to premature obliteration of specific sutures. The interesting work of Mount (50) is significant. He removed surgically from the heads of young scaphocephalics with deformity strips of bone along the obliterated sagittal suture line. He obtained relief of the deformity with a new suture being formed at the proper line of coalescence in the new bone which grew in to cover the defects produced by the removal of the strips. The problem of the significance of sutures and their closure still requires further elucidation.

Cranial texture

Age changes are also evident in the texture and markings of the cranium both without and within.

The texture of the young adult cranium is ivorine in both outer and inner surfaces but gradually, between thirty and fifty years, a change takes place. The surface assumes a matté appearance like that of an English biscuit. It is not coarse enough to deserve the term granular, though granularity may occur after middle life, and is often present in advanced

age as evidence of nutritional deficiency. The muscular ridging on the exterior of the cranium, absent in the young, shows itself in temporal and occipital areas from twenty-five years. It does not become better marked during mature life nor does it diminish in advanced age. Similar muscular ridging appears and pursues an identical course on zygoma and masseteric area of mandible. Pitting of the parietal bones is not an age character but is evidence of a nutritional defect in childhood. From this the bones, once scarred, never recover so that the percentage showing pitting remains approximately constant in samples no matter what their age. The imprint of the sagittal venous sinus does not become more marked during mature or even advanced age nor does that of the left lateral venous sinus though there is some evidence, perhaps equivocal, of deepening in the imprint of the right lateral venous sinus after fifty years is reached. Contrary to general belief no significant change has been found occurring solely as a result of advanced age in depth or extent of Pacchionian depressions. The grooves for the meningeal veins (32) do however show a deepening and sharpening of their margins as age increases.

Symmetrical atrophy of the parietal bones has been claimed as an age characteristic since Maier first adequately described it (47). It is however by no means frequent. Humphry ((28), pp. 242–243) found only one example in Cambridge, four in Paris and one in Berlin and hazarded, from the exact symmetry, similarity of deficiency in the several skulls and from the absence of any trace of disease, that the condition is congenital The review and experience of Wilson (92) confirm the infrequency of the condition and the lack of evidence for identifying it as an age change. Among more than 2600 contemporary skulls of white and Negro origin added to the Hamann Museum since 1912 it has never been seen, but it does occur once only as a well marked feature among the skulls collected for the Museum from the unclaimed dead of Cleveland since the year 1892. This skull is figured by Keen ((34), vol, 3, p. 43). Symmetrical thinning of the parietal bones was very common in Egypt between the fourth and nineteenth dynasties, occurring among the upper classes in people accustomed to wear wigs of enormous proportions and great weight (59). It is produced by a thinning successively of the outer table, diploe and inner table and never occurs under about thirty years of age. Meyer (49), writing ten years after Elliot Smith, has doubts on the uniformity of causation but there was no history for any skull in Meyer's series to give indication of a probable cause. The skull (0.22 W.R.U.) in the Hamann Museum illustrates the fact that in symmetrical thinning of the parietal bones we may have to deal with diverse causes. Thinning in this skull started on the endocranial surface which shows sheaves of vascular channels radiating from the sides of the sagittal elevation along which the sagittal venous sinus coursed.

Some of these are associated with Pacchionian depressions. The diploe has collapsed but the outer table is not directly affected. Meyer's contention is therefore borne out, but this is a totally different type of thinning from that described by Elliot Smith. It is however equally pathological in origin and in no way a feature of age.

Wetzel (91) speaks of an atrophy of diploe in old age. Schüller (57) however describes this change as a transformation of the diploe into bone from fifty years onward. He also claims as age characters both symmetrical thinning of the parietals and general thickening of the vault. In his very large collection of skulls of known age Todd showed that there is no characteristic change in the thickness of the vault with advancing years. If there is a real and constant change in cranial thickness characteristic of age it is not conclusive enough to permit measurements.

The diploe of the cranium, which first makes its appearance in childhood at about the sixth year, continues to develop until young adult life and is evident in the roentgenogram as a fine mottling. Harris (25) has pointed out that the diploe first becomes channelled by venous sinuses at about thirty-five years, possibly to provide a back-water connected with the cerebral circulation as these diploic sinuses form a communication between the venous sinuses of the dura and the veins of the scalp. Harris further points out that after the onset of the menopause in women and during the later fifties in men the diploic sinuses again disappear with the increase of bony deposit in the diploe. This of necessity means a reduction and final elimination of the safety factor provided for middle life by the presence of the diploic sinuses. The fine mottling on the roentgenogram now gives place to a more irregular open tracery or complete loss of mottling.

Halisteresis has frequently been described, both in cranium and face, as characteristic of old age. It is by no means invariable and is definitely an expression of the failure of adequate nutrition which so often supervenes as a mark of infirmity in the supportive tissues of advanced years. Pearce (51) has described the diminution in oxygen consumption of excised organs in mice of a year or more in age when contrasted with the tissue respiration of growing animals of the same racial strain. No such experiments are extant to demonstrate a like distinction in bone or connective tissue. But Wolbach's researches on the influence of Vitamin C in the formation of collagen and reticulum (48, 93–95) together with the investigations by Lanman and Ingalls on the resistance of healing wounds to the strain of rupture make very impressive the indispensibility of Vitamin C for the effective function of connective tissue. Good bone texture of proper strength is likewise the result of appropriate nutrition in adequate amount and suitable form. The infirmities of old age, implying malnutrition in diverse forms, are certainly associated with halisteresis. Further an osteoporosis

indistinguishable from the halisteresis of advanced years is frequently present in persons of mature and even of youthful age when suffering from chronic impaired constitutional health. Many fractures of the skull are due less to the force of the injury than to the weakness or brittleness of the osteoporotic bone.

A study by Todd (69) of the thickness of 448 male white crania indicated that there is a slight increase in thickness up to about 60 years with no change thereafter. Cranial thickness is, however, so variable that it appeared *un*reasonable to believe under specific natural control. A relationship between thickness and capacity was suggestively indicated, the more capacious crania being thinner. Because thickness is too variable to permit prediction of change with any real accuracy for a particular skull, it appears to have minimal value as an age indicator.

Scapula

Age changes in the skeleton can clearly be seen in the thin translucent scapula. These changes resolve themselves into three types, namely, modifications of vascularity, of surface texture, and of cancellous structure. For information on vascularity and surface texture we are indebted to Graves (23).

The features of deep vascularity in the bone substance are best shown in photographs made by transmitted light which demonstrates also the atrophic spots in surface texture. Surface vascularity is easily seen by simple observation but the vascular tracks are small and the history of their modification is identical with that of deep vascularity.

Figure 11 shows the vascular pattern in adolescence. It is rich over entire noncancellous areas both above and below the spinous process. In the early twenties (fig. 12) it is equally rich but its pattern is more distinct. Leashes of vessels sweep over the axillary and vertebral borders and swirl inwards and downwards from the region of the spinous process. In the infraspinous area leashes also enter through the glenoid base swirling upwards and downwards respectively to mingle with the leashes sweeping over the axillary and vertebral borders.

The lines of attachment of intramuscular tendinous bands are evident as narrow dark zones originating in the vertebral border and extending towards the glenoid base. By about the age of fifty years (fig. 13) the vascular pattern is no longer clearly marked. The lines of tendinous insertion are more numerous and between them are clearer, irregular areas of bone atrophy. In old age (fig. 14) deep vascularity is distinguishable by transmitted light and the thickened ridges of tendinous attachment appear as dense black zones extended into a bizarre pattern of local thickenings between which are the clear atrophic spots.

The surface texture of the bone changes with advancing age in a manner similar to that of the skull. In the thin scapular blade these changes are complicated by the appearance of areas or spots of atrophy, seldom seen before forty-five years but occurring with increasing frequency after fifty years. The bone, held up to the light, seems patchy, spotted or "moth-eaten". Those areas in which the atrophy is more advanced are depressed below the level of the adjacent surface and plainly delimited by a sharp





Fig. 11 Fig. 12

Fig 11 Transilluminated scapulae No. 633 W. R. U. Negro, female, aged 13 years. Note richness of deep vascularity as described in figure 12.

Fig. 12. Transilluminated scapulae. No. 423 W. R. U. White, male, aged 21 years. Leashes of vessels sweep over axillary and vertebral borders and swirl upwards and downwards from region of spinous process.

margin. By transmitted light the spots are pearly, granular and amorphous in appearance. They may be thin like parchment or their centers may be perforated. Thus they resemble the special symmetrical atrophic areas on the parietal bones.

Accompanying the bone atrophy are other features, namely, blistering, buckling or pleating of surface and distortion of substance. A coarse wrinkle or pleat may be seen even in the thirties. It usually appeared on the dorsal surface of the blade below the spine and parallel in a general way to the cristae of tendinous attachment. Buckling is more frequent in thin blades and increases in frequency with age. Blisters are local areas of paper-thin compacta raised above the surrounding surface. They cover venous en-

largements and are seen only in advanced age. Distortion implies deformity or warping of the entire thickness of the blade. It can be seen equally well in macerated and in fresh dissected scapulae of advanced age but never occurs in scapulae possessing a thick blade.

All the foregoing characteristics of age can be seen in roentgenograms of the scapula but they are less clearly evident than in transilluminated bones.



Fig. 13



Fig. 14

A roentgenogram of the scapula is particularly instructive for the study of cancellous tissue. This is illustrated by figures 15–18.

In adolescence (fig. 15) there are no cristae of tendinous attachment. Thickening has not yet taken place on the axillary border. Cancellous tissue is close textured with fine trabeculae along borders and attachment of spinous process. Lacunae of more open trabecular architecture occur between axillary border and spinous process. Trabecular lines paralleling glenoid surface have appeared in glenoid base but those radiating from glenoid surface have not yet arranged themselves into a formal pattern.

During early adult life (fig. 16) cristae for tendinous attachment are

commencing to develop and the axillary border is thickening. Cancellous tissue is close textured; its trabeculae and lacunar formation are unchanged from those of adolescence. The trabeculae parallel to glenoid surface in the glenoid base are also unchanged; the radial trabeculae have now arranged

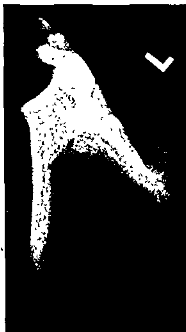


Fig. 15



Fig. 16

is not yet formed.

Fig. 16 Roentgenogram of left scapula. No. 680 W. R. U. White, male, aged 23 years. Vascular pattern is less rich but more formal in design. Cristae of tendinous attachment are commencing. Axillary border is thickened. Cancellous tissue is close and fine textured along borders. Lacunar formation remains as in figure 15 Radiating lines are arranged in formal pattern in glenoid bone. Lines paralleling glenoid surface are the same as in figure 15. Glenoid rim is not yet formed.

themselves into a formal pattern. The glenoid rim, which is not evident until about thirty-five years, is absent.

During mature life, except for a possible further development of cristae, there are no significant changes in substance.

With the onset of old age (fig. 17) cristae for tendinous attachment are numerous and well developed. Cancellous tissue becomes more open and its lacunar formation becomes more extensive. Irregular areas of atrophy

with surface pleating are evident. The articular margin of the glenoid surface no longer shows a beaded rim but has a sharp lipped margin. There is reduction in thickness and number of parallel and radiating trabeculae beneath the glenoid surface.



Fig. 17



Fig 18

the spine

In senility all the features of old age are accentuated but if halisteresis or demineralization becomes severe (fig. 18), as it often does in advanced age, all the features already catalogued as characteristic of old age and senility become exaggerated except the cristae which cannot become sharper or more pronounced for lack of mineral.

These observations are, to a certain extent, heterodox. It must be remembered, however, that intensive study of age features in the skeleton

was impossible until the utilization of the roentgenogram as a routine technical method for study and the establishment of the collection of skeletons of known age in the Hamann Museum. Cristae are not evidence of muscularity but merely of maturity. Whatever the influences which determine the formal pattern of bone architecture the pattern itself is an age character developing in childhood and youth, maintained during mature life and lost as age advances or infirmity intervenes.

Articular lipping

The phenomenon of articular lipping has already been mentioned in connection with later pubic differentiation and ageing in the scapula. It has been stated to occur also around the margins of the joint surfaces of the long bones, vertebrae and ribs. Unfortunately, a definitive treatise on the subject has not been written.

Willis (92) reported upon the changes found in the lumbar vertebrae of 625 columns in the Reserve collection. It had been observed that the lumbar region was especially subject to these changes.

Lipping is not specifically defined but it seems reasonably clear that the reference includes any ligamentous ossification or new bone formation at the capsular line of a joint, a condition which is clinically labelled hypertrophic arthritis.

Up to age 35, practically no lipping was encountered. After age 45, however, the condition was universal and progressed with further advance in years. The frequency distribution according to degree of lipping showed gradual and uninterrupted progress with age.

As earlier authors had indicated a relationship between body build and hypertrophic arthritis, Willis classified his columns as to structural type as, slender, average and heavy. In the series of 625 spines, the average type was the most common, followed closely in frequency by the slender. The heavy type was decidedly less abundant than the other two. In age incidence, the slender type dropped out 15 years earlier than the others. This was said to be, "probably due to the fact that in advanced age the erosion of the vertebral bodies and the lateral lipping increases the width of the body in relation to its height, the segment therefore assuming a heavier type of appearance."

It was found that no type was immune to the process of lipping, but that there was "a distinctly stronger tendency (for it) to progress in inverse ratio to the vertebral index of the individual", that is, the heavier types were more susceptible to the change. Lipping, though just as invariable, tended to occur about a decade later than in the slender type.

This finding suggests function rather than age as the fundamental causative factor in this change, even though it be of universal occurrence after

age 45. Willis comments in this connection that, "we have the clinician describing the bone changes of the 'chronic rheumatism of the elderly' as necrosis in the vicinity of a joint with irregular laying down of new bone at the capsular attachments, while the anatomist describes age changes in the bone as a rarefaction and erosion with erratic ossification. The difference then must be one of degree or of arrangement. Theoretically the age influence is exerted steadily and continuously but is necessarily affected by general habits of life and general physical condition. Its 'lipping' should be 'regular.' The pathologic influences, variable in severity and in continuity, exerting an erratic and spasmodic influence, should result in bizarre lipping with sclerosis and osteoporosis of the bone, not seen as a result of age influence alone."

Keefer, Parker, Myers, and Irwin (33) have shown that changes occur in increasing frequency with advancing age at the knee joint. These changes are identical in both sexes. They are commonest in areas subjected to movement, strain, weight bearing and injury. They bear no relation to symptoms, to arteriosclerosis or to other particular disease processes. In the one hundred knee joints studied by these four authors age changes occurred in the patella in 81 per cent, trochlear surface 65 per cent, lateral *condyle of tibia 64 per cent, medial condyle of 55 per cent, medial condyle* of femur 43 per cent and lateral condyle of femur 36 per cent. The same authors state that the synovial membrane was essentially normal except in joints which showed changes in the cartilage. In these the capsule was thickened: there were papillary projections of synovial membrane and occasionally small collections of lymphocytes around the blood vessels. Changes in the cartilage comprised fibrillation, degeneration, destruction and in some areas regeneration such as Amprino and Bairati (3) have described. Subarticular bone was thickened. Marrow spaces were frequently filled with fibrous tissue. Cysts and areas of cartilage were present in the bony tissue. There were also exostoses and projections of cartilage over the margin of the joint surface and depressions of cartilage below the original level which was caused by flattening or erosion of the joint surface and which gave the appearance of bony outgrowth. All these changes, which are identical with those of degenerative or hypertrophic arthritis, were found to occur in increasing frequency with advancing age. The initial features of rim formation and lipping, to which reference has already been made above are to be found in the article by Graves (23).

The facts indicate that lipping is a phenomenon due primarily to metabolic alteration which results in ossific deposit where there latter does not normally occur. To some undetermined extent this alteration is associated with age, but the distinction between ageing and pathological excess cannot yet be made. Further secondary changes of a functional nature due to the

primary metabolic alterations, as in osteoporotic weakening of the vertebrae, may be identified with age but are not causally related to it in the first instance.

These conclusions are confirmed by the excellent study of age changes in the knee joint by Bennett, Waine and Bauer (9) based on examination of specimens from 63 individuals from one month to 90 years of age, none of whom had had symptoms of joint disease or evidence of joint abnormalities on physical examination. The gross specimens were fixed when fresh, after amputation or autopsy, and gross and microscopic findings were carefully recorded and photographed. These authors found that in every subject beyond age 15, some degeneration of the knee joint was observable.

In their subjects of 15 year or younger, the peripheral margin of the entire tibial epiphysis and that of nearly all the femoral epiphysis were covered by a layer of hyaline cartilage nearly as thick as the articular cartilage. In the subjects between 15 and 20 years, this cartilaginous covering was no longer present, indicating cessation or marking slowing of lateral growth. In subjects of the third decade, the perichondrial margins of the femoral condyles were found sharply outlined, somewhat elevated and nodular, but no evidence of abnormal overgrowth to warrant the designation of marginal lipping.

In a specimen of the fourth decade a small triangular "spike" on the tibia composed of subchondral bone and calcified cartilage was noted extending to the joint surface at the margin of the lateral condyle near the tibial eminence. Microscopic study suggested that it had arisen from proliferation of vascular connective tissue of the subchondral marrow spaces through a gap in the calcified layer of cartilage and into the substance of the deteriorated cartilage. This lesion was the earliest definite example of lipping encountered by Bennett and his associates in their series.

In the fifth decade lipping was not found on any of the tibial condyles but in some instances was well marked around those of the femur. In this age group the first case of loss of all cartilage from an eburnated epiphysis was observed.

Beginning with the seventh decennium it was rare that any one of the articular structures was found normal. Marginal lipping was present in each instance around the patellar surface of the femur.

In specimens of the eighth, ninth and tenth decades, without significant exception, the average pathological change in each subdivision of the joint had increased. The order of magnitude remained nearly the same. Thus the patella, patellar surface of femur, exposed areas of the tibial condyles and the portions of the femoral condyles subjected to heaviest use, exhibited the greater measure of degenerative and hypertrophic alterations.

While giving due emphasis to the obvious significance of functional con-

siderations, in an exhaustive review of etiological factors, Bennett, Waine and Bauer did not essay fundamental explanations of their own. Degenerative joint disease is frankly a pathological process, not *per se* an age change, but the most important correlative with this process, they showed conclusively, was increasing age. In their opinion, morphological data alone held limited opportunity for further advances, but the combination of microscopic observations with histo-chemical methods and studies of tissue metabolism was promising. The recent developments with ACTH and cortisone emphasize the importance of experimental method in this connection.

Density of bone

The density of bone bears an obvious relationship to its functions of support and mineral storage. The general awareness of age variation in density is reflected in lay reference to the green-stick nature of the bones of the young and the brittleness of the skeleton of the elderly. Ingall's study of bone weight (31), involves the largest number of individuals of any investigation related to the subject. Ingalls weighed the entire skeleton and individual bones of 100 male whites, comprising 20 cases each in the 5 ten year age periods, 19–30, 31–40, 41–49, 50–59, and 60–78 years.

The total skeletal weight showed a rise from about 25 to 35 years, followed by a decrease to a point a little below the mean at 45 years. From this period the curve rose to its highest value at 55 years and sloped to its lowest point between 65 and 70 years.

The initial rise to 35 years, Ingalls considered the end of the post pubertal rise in general bodily dimensions. In bone weight there is a peak in bone development around 35 years, when the skeleton "is in its prime, full blown". After this peak there is a decline which "marks the beginning deterioration of bony tissue, the first real age change, a gradual lightening of the bones, an increase in their porosity and an accentuation of some of the finer surface markings. In a word the bone is past its prime and those physical characters which enable it to perform its functions and determine largely its specific gravity and weight, suffer a gradual recession from the previous high water mark."

The second rise in weight to the maximum weight at 55 years is held to be spurious, "in that it does not indicate a return to normal, earlier conditions, but is much more like a degenerative or pathological process. It is accounted for by the formation of new bone, as around articular surfaces, and is also especially marked in the skull and axial skeleton where it may assume some importance.

"The final fall in bone weight carries the total skeletal weight to its lowest point, the bone has become light and porous, it has lost much of its

original elasticity and capacity for resistance and the margin of safety may quite or almost disappear. This is the well known senile atrophy which, however, does not affect all of the bones of the body in the same way; it closes the story of bone development."

The several parts of the skeleton vary somewhat in the degree and time of their manifestation of the general pattern of age change just presented. The influence of a given part on the age picture will be affected by the proportion it contributes to the total skeletal weight. Ingalls gives the following figures:

Lower extremities	47%
Upper extremities	19%
Axial skeleton	19%
Skull	15%
Entire skeleton	100%

Obviously the lower extremities will influence most markedly the age pattern.

Two elements, the skull and the sternum show an increase toward the later end of the life span. The progressive increase in skull weight occurs in spite of the loss of teeth and associated alveolar bones. The increase definitely involves the cranial vault, as shown by Todd's study on cranial thickness, and probably the face, especially in the male, contributes in those features which make for ruggedness and massiveness in appearance.

The vertebral column shows an increase in weight to 35 years, followed by a loss to less than mean weight which obtains until 55 years after which there is a rise in later life similar to that in the skull.

"There appears to be some loss in weight from the thirties into the forties and hypertrophic changes are more than outweighed by atrophic changes elsewhere in the bone. Beyond this time the weight is increased and maintained, except for the thoracic spine, and the senile atrophy, so common in most bones, is either less in evidence here or counterbalanced by new bone formation."

"The thoracic spine is both absolutely and relatively the heaviest portion of the column. It shows also the greatest changes with age. Beginning with only 94.2% of its mean weight it increases by more than 7% in the next ten years to 101.4%. It then drops off to 99% but rises in the fourth decade to its maximum of 103.7%. The total range of 9.5% is higher than in any other region of the spine and is practically identical with the range exhibited by the skull."

The sternum and ribs contrast markedly, the sternum showing progressive increase in weight throughout adult life and the ribs show an almost

continuous decrease over the same period. Trotter (88) found no age relationship in the incidence of synostosis between the manubrium and body of the sternum in a series of 877 sterna of whites and American Negroes.

Ingalls believed that "the continued rise during adult life and with advancing years may be only the sternal reaction to age, as in the skull, aggravated perhaps by the association with the sternum of large amounts of fibrous or tendinous tissue."

The ribs, clavicle and tibia are the only bones which show maximum weight so early in life. Ingalls ascribes the age pattern to rib weight to functional requirements because of their intimate association with respiration.

Because of the percentage of total skeletal weight which they form, the age changes for "the entire skeleton are for the most part the expression of the fluctuations occurring in the bones of the limbs. . . The great weight of the lower extremities, and especially of the pelvic girdle, is a large factor in bringing about this result."

In the upper extremity the greater weight of the right limb has no interest in the matter of ageing. When asymmetry, either functional or structural, is present in the lower limb, it is much less marked than in the upper.

The evidence of age changes in bone weight and cranial thickness is, therefore, to the effect that such changes are very real but individual variability is very great. Data are still too few.

Mineralization

Inasmuch as age changes in the density of bone cannot be reliably determined from dried specimens due to the varying effects of the preparatory process and other factors the study of living tissue by means of the x-ray has been necessary for this purpose. It is noteworthy that Wingate Todd envisioned clearly the value of studies on the living of known status for showing the effects of nurture and genetic factors. The very extensive series of studies of growing children and adolescents carried out under the Brush Foundation in Todd's laboratory have provided much information of value in offsetting the lack of birth certificate ages on the adult skeletons. Such studies, in the nature of the case, must constitute a series of revisions, the results of each study indicating the next to be carried out. In this way Stevenson's (60) study of epiphysial union based on cadavera was eventually replaced by Todd's standards made from roentgenograms and the first volume of an atlas (76). The latter in turn has been succeeded by a further revision taking into account puberty and other influences not fully evaluated in the preceding studies (24).

The same procedure will be necessary in studies of ageing in the adult skeletons, even those limited to the description of morphological features, because the problem is more complex in the adult than in the preadult. The active biochemical changes constantly evident in the skeleton at all ages are reflected in the equally changing structure detectable both by roentgenography and by histological examination. Haversian systems, formerly thought to be characteristic of compact bone, were shown in 1913 to be present also in spongiosa or cancellous tissue (62), an observation later confirmed by Arey (5). But haversian systems whether in compacta or spongiosa are not permanent: they undergo resorption and replacement with or without the accompaniment of osteoclasts (62). During pregnancy and the first six months after parturition, during infancy and adolescence, subsequent to fracture or bone disease, and in injuries of the soft tissues such as complete severance of median nerve or the tendons at the wrist, changes in mineralization of spongiosa have been observed to occur so rapidly that within six weeks the difference may be clearly evident in the roentgenogram. Analyses of the second phalanx of the little finger from hands of which roentgenograms have previously been made, show that a difference in structure discernible to the naked eye on the roentgenogram corresponds to a difference of 25 per cent in the amount of mineral per unit volume of bone. Lachmann and Whelan (42) have stated that a difference of 7 per cent can be detected by roentgenography on dead bones experimentally subjected to the local action of acid. This is not strictly comparable to the process of demineralization of halisteresis during life (76).

The degree of fluctuation in mineralization occurring in the ordinary vicissitudes of life is illustrated by selected roentgenograms of the left wrist (figs. 19–21). These show respectively, the amount of mineral in the bones of the mother of one of the children in the Brush Foundation series the day before delivery, three months after delivery (the baby being breast fed for two months), and six months after delivery. In a well mineralized bone the interstices between the trabeculae of the spongiosa are filled with a gray sheen of labile mineral which to some extent obscures the tracery of the trabeculae. Owing to the demands of mineral for lactation, this gray sheen is less evident three months after delivery but is restored in another three months. Changes in the trabeculae themselves are limited to modifications of thickness and occasional fragmentation. Figures 22–26 typify the changes in bone texture characteristic of healthy life from adolescence onward and the demineralization incurred in constitutional deficiency. They demonstrate the hand textures of adolescence in a healthy girl of 13 years, in a girl of the same developmental age having a constitu-



Fig. 19 Fig. 20 Fig. 21

Fig. 19. Roentgenogram of left carpus. X-6714 A. White, female, aged 28 years. The day before delivery. Mineralization somewhat light. Interstices of trabecular tracery filled with gray sheen of labile mineral Metaphysis of radius fairly uniform in its gray sheen.

Fig. 20. Roentgenogram of left carpus. X-6714 E. Same woman. Three months after delivery. Mineralization reduced. Interstices drained. Trabeculae stand out more clearly. Metaphysis of radius has lost gray sheen near epiphysial line.

Fig. 21. *Roentgenogram of left carpus.* X-6714 G *Same woman.* Six *months after delivery. Mineralization restored. Interstices* once more filled with gray sheen. Metaphysis of radius also shows restoration of sheen

tional deficiency, in a healthy woman of 27 years, in advanced age and in the constitutional deficiency which usually accompanies senility.

In a healthy girl (fig. 22), a gray sheen largely obscures the trabeculae, the tracery of which is well on the way to adult pattern. Compacta is



Fig. 22



Fig. 23

[illegible]

complete.

dense though still thin in radius, ulna and metacarpals and incomplete in phalanges as one expects of a child. Spongiosa of shafts of radius and ulna, of carpals and of metacarpal heads and bases already shows the closely arranged, fine trabeculae and interstitial gray sheen of labile mineral in normal adult life; but in phalanges, epiphyses and distal parts of metacarpal shafts it has not yet attained the adult pattern. Ossification is nearing completion in the sesamoid of the little finger. The dense outlines of the bilateral bosses on metacarpal heads have not yet spread to the shafts. Radiating trabeculae are arranging themselves beneath articular surfaces but the surface outlines themselves are not yet dense nor are they accompanied by subjacent parallel trabeculae.

In the girl nineteen years of age but of retarded adolescent development and of constitutional deficiency (fig. 23), the trabecular pattern is almost identical with that in figure 22. The gray sheen has however largely disappeared from the interstices. The compacta of radius, ulna and metacarpals is lightly mineralized and thin. It is very light and retarded in development in phalanges. Spongiosa of radius, ulna, carpals and metcarpals *shows a more open tracery of thicker trabeculae, fragmented indeed* in places such as lower radius, its epiphysis and the carpals. In the tracery are irregularly scattered "knots" or little nodes of denser tissue. These are characteristic of bones in which restoration of adequate mineralization is still possible. One might define the condition as reversible halisteresis. We have not found these knots in the halisteresis of advanced age. A somewhat similar course of remineralization has been described by McLean and Bloom (45) in experimental studies on the effect of parathormone in young growing rats. Trabeculae and knots are the more obvious because of the lack of interstitial labile mineral. Sesamoids, despite an outline characteristic for the age, show halisteresis. The outlines of bilateral bosses on metacarpal heads are also poorly mineralized. The radiating and parallel trabeculae under articular surfaces show a development characteristic of the stage in physical maturation.

The hand of the adult woman (fig 24) shows the closely arranged fine trabeculae and interstitial gray sheen characteristic of health. Compacta is dense, thicker than in adolescence and is now well developed in all phalanges. The sesamoid for little finger is fully ossified. The bilateral bosses on metacarpal heads have dense outlines extended on to the shafts. All articular surfaces are densely outlined and present a full complement of subjacent radiating and parallel trabeculae. The dense outlines of articular surfaces on carpals are somewhat obscured by the interstitial sheen.

In the hand of advanced age (fig. 25) there is thinning and some de*mineralization of compacta in all bones but the articular surfaces main*tain their shell of dense tissue. Halisteresis is evident in all sesamoids. No

reducation of density has occurred in the outlines of the bilateral metacarpal bosses. The subarticular parallel trabeculae have almost disappeared





FIG. 24 FIG. 25

FIG. 24. Roentgen[illegible]

ing and parallel trabeculae.

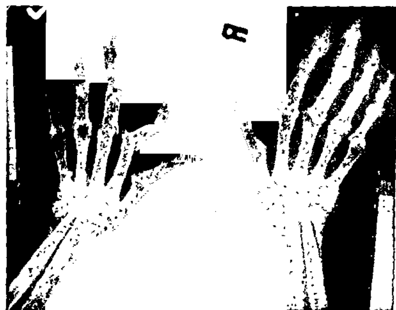
FIG. 25. Roentgenogram of left hand in healthy advanced age. White female.

except in lateral part of metaphysis of radius.

but the radiating trabeculae, though thin, maintain their formal pattern. Trabeculae of spongiosa are thin but not fragmented: they are not thick as in the demineralization of adolescence.

The skeleton of advanced age complicated by constitutional deficiency

(fig. 26) presents a very different picture. Clinically it would be described as polyarticular atrophic osteo-arthritis. Compacta is paper-thin or entirely absent. The dense compact tissue of the articular surfaces is reduced to a mere shell or has completely collapsed with consequent telescoping of bones and formation of exuberant articular flanges. Trabeculae in the spongiosa are very thin, are fragmentary, have completely lost their for-



mal pattern and show no "knots". The gray interstitial sheen is almost entirely lacking.

Roentgenographic analysis of skeletal texture requires an adequate knowledge of bony structure in health and age but the reading of roentgenograms is greatly facilitated if proper precautions have been taken to insure uniformity of technique in processing (76).

The gray interstitial sheen of labile mineral has not previously been emphasized by other writers but Bauer, Aub and Albright (7) noted a diminution of trabeculae in kittens shortly after birth. They concluded from this that calcium is stored in the trabeculae against demands of

postnatal growth. Burns and Henderson (13) found this true also of cortical bone. Bone growth, they say, is largely determined by local factors, and not wholly by systemic blood supply. During growth bone is in dynamic equilibrium with its tissue fluids. This theme of bone change can be applied equally well to the phenomena of ageing. McCay, Crowell and Maynard (44), describing the effect of retarded growth on the length of the life span, observed that the aged bones of their retarded rats were all demineralized despite the adequate ration for nutrition which they were careful to supply.

That there is a change in the collagenous matrix (91) of demineralized bone is evident from the brittleness of these bones. Intracapsular fracture of the neck of the femur is a good example: it usually occurs in the aged but may be seen also in children. Fracture of the bones in fragilitas ossium is another example. Probably the claim that 50 per cent of all fractures of the clavicle occur in children under five years, and the ease with which fracture of the skull occurs in some adults, are to be attributed to this brittleness. So many instances of greenstick and crushing fracture occurred in the inadequately mineralized bones of allergic patients in Todd's experience that he believed this type of fracture should be considered a definite hazard of allergic children. Halisteresis however does not imply nonunion after fracture. The bony callus for repair of fractures is obtained though indirectly, from the adjacent areas of the shaft even though that shaft be relatively demineralized.

A study of ununited fractures shows that no rarefaction occurs in the neighboring areas of the shaft subsequent to the injury. This failure of adjacent bone to give up its mineral to the callus is not confined to the skeleton of advanced age. Nonunion is likewise to be found in fractures during infancy and even in "intra-uterine" fractures. Inasmuch as repair of demineralized bones readily takes place, there can be no impediment in these bones to cellular proliferation or to the normal biochemical processes of bone formation.

One of the characteristic features of advancing age is the increase in number of collagenous fibers (91). But if, as a result of constitutional deficiency, this does not happen, the matrix of white fibrous tissue in bone will be imperfect, perhaps replaced by some liquid material. The process suggests a deficiency of Vitamin C and, though vitamin deficiency has not so far been shown to be characteristic of ageing, it is certainly present in many old people (56). The fact that the rats utilized by McCay, Crowell and Maynard (44) showed demineralization despite an adequate ration is not inconsistent with this view. We know very little of the changing needs of the ageing organism for the several nutritionals.

Details of interrelationship between the biochemical factors and the

histological elements in bone substance are still obscure. Radio-active tracer substances may provide useful information in this area. That bone is in a state of constant change, however, is illustrated by the investigations of Chiewitz and Hevesy who, using as an indicator the radio-active isotope of phosphorus P^{32} which has a half-life of seventeen days, found that the average time spent by a phosphorus atom in the body of a normally fed rat is about two months. Their rats, killed about a month after the intake of phosphorus, contained only about half the active phosphorus found in those killed at the end of a week. About 30 per cent of the phosphorus deposited in the skeleton of the adult rat seems to be lost by the end of twenty days. Calculations of the phosphorus content of the different organs per gram of dried tissue showed the spleen and kidneys contain about 18 per cent, brain nearly 15 per cent and liver 14 per cent. Muscles and fat contain 7 per cent but bone a little less than 3 per cent, despite the fact that the larger part of the phosphorus ingested goes into the skeleton. No conspicuous differences are found in the phosphorus content of different parts of the skeleton. On this analysis the bones are continuously taking up atoms of phosphorus which are wholly or in part lost again and are replaced by others, the phosphorus temporarily stored in the sketeton being utilized in the metabolism of organs.

Housing of Hemopoietic Tissues

The role of bone in hemopoiesis is entirely passive. The red marrow or hematopoietic substance merely finds shelter in the marrow cavities and cancellous spaces of the bones, although in those spaces which house blood forming tissues, there is progressive diminution of bony trabeculae as age advances and red marrow changes into yellow. The study of Piney (54) of material from 91 subjects between the ages of 3 days and 83 years affords the most comprehensive information on the subject of age changes in the red marrow. At birth and during the first 3 or 4 years of life red marrow is found in the cancellous spaces of both epiphyses and metaphyses, as well as the medullary cavities. Beginning at about age 7 there is a progressive diminution of the hematopoietic stations in both epiphyses and diaphyses. At about the time of cessation of growth or epiphysial union in man, the metaphysis usually loses its capacity to form red blood corpuscles The different metaphysial stations of the long bones thus automatically retire in succession during adolescence, but patches linger on into adult life in the upper end of humerus and femur. Remaining also in adult age are the stations in ossa innominata, bodies of the vertebrae, ribs and sternum. Piney found that in the ribs the marrow adjacent to the cartilages usually becomes fatty about age 25 for a distance of about an inch. The marrow of the vertebrae tends to remain red throughout life.

In no case was fat found above the third vertebra. The change to fatty marrow appears to begin below and proceed upward. Fatty change is more conspicuous in the upper sacrum and fifth lumbar vertebrae than in the third lumbar. This has interest in connection with the observation of Ranvier that animals lose red marrow first in the caudal vertebrae.

Analysis of Recorded Age Estimates on the Reserve Collection

A comparison of the stated, estimated and skeletal ages of the skeletons in the Reserve collection will provide the best index available of the present status of our knowledge of age appraisement on the adult human skeleton.

For *each* skeleton in the Reserve collection there is recorded a *stated age*, which appeared on the death certificate of the cadaver when brought to the laboratory. For *most* of the skeletons there is listed an *estimated age*, which represents the opinion of Professor Todd as to the age of the individual judged from the extrenal appearance of the cadaver at the time it was received. For a large number of the skeletons there is also on file an assessed *skeletal age*, which also represents the considered judgment of Professor Todd after a complete examination of the macerated skeleton and appraisal of all available history.

Error must be presumed inherent in the respective series of stated, estimated and skeletal ages.

Error in the *stated ages* derives from the following factors: 1) for many individuals the age recorded represents only a coroner's or an undertaker's estimate, because the persons were found dead, and being unknown and unclaimed, there was no source from which an authoritative statement could be obtained; 2) many people, particularly of the social stratum from which the cadavera were conscripted, do not know or tend to forget their exact age; 3) when a post-mortem examiner estimates a person's age, or when a living individual has to estimate his own age, they tend to give it in terms of the nearest multiple of five (16, 18, 70).

The *estimated ages* involve error, first, in that anyone may look older or younger than he really is, and second, in that these estimates signify only the subjective opinion of a single examiner. Although these are admittedly carefully considered appraisals based on a large experience, there exists no recorded series of estimates of ages of individuals of known age by this examiner which could be used as an objective check on the accuracy of his estimations.

In a trial series of 26 cases Todd and the writer independently estimated the ages of the same cadavera on admission to the laboratory. The estimates of each examiner were compared with the stated age, on the as-

sumption that the latter had at least some historical basis. The results of this meager and necessarily inconclusive exploratory series suggest that it is definitely better to have 'estimated' ages than not to have them, but that no great reliability can be assigned them.

In 20 of the 26 cases (77 per cent), the estimates of one or both observers either coincided with the stated age, or the estimates of both observers varied from it in the same direction and generally to about the same degree. In more than three fourths of the cases, therefore, both observers recorded approximately the same age *impression* of a cadaver. Hence, if a stated age were incorrect, the estimated age would be more likely to record a truly corrective impression than not to do so. In six of the cases the observers varied in opposite directions, one believing the cadaver older or younger than stated age and the other younger or older. In the entire series the senior observer more frequently estimated the cadavera younger than stated (15 cases) and the junior more frequently appraised greater than the stated age (14 cases). Of the 6 cases in which the disagreement was in opposite directions, the senior observer recorded a lesser than the stated age five times and a greater once, the reverse being true for the junior observer. *The personal equation thus is clearly an element to be evaluated in any series of estimated ages.* The data presented afford no proof as to which observer should be considered the more accurate. The greater experience of the senior observer would impute, though not establish, a greater reliability for his estimates.

The error in the *skeletal ages* may be attributed principally to two factors. First, the maturity determinators on which the assessments are based can be regarded as proved only in respect to sequence in developmental pattern and not as pertains to chronological association. Second, the incidental fact that the later skeletal assessments were based on greater experience and more advanced technique than the earlier and hence might be presumed to be more accurate.

In 1932 Todd followed the routine of recording his assessment of the skeletal age on a card in the form of a condensed descriptive statement, in which the condition of several determinators was cited. These determinators were the sutures, pubic bones, teeth, articular margins and the bony texture and weight, plus indicated miscellany. This is the form in which most of the skeletal ages are recorded.

Todd's confidence in the accuracy of the skeletal age was manifest in the specific statement generally made on the assessment record concerning the validity of the stated age as determined by the bone examination. The following eight characterizations were used: (a) stated age certainly correct; (b) stated age approximately correct; (c) stated age probably correct; (d) stated age probably approximately correct; (e) stated age

probably a guess but may be correct; and, (f) stated age certainly incorrect; (g) stated age very probably incorrect; (h) stated age certainly a guess.

The very critical judgment and analysis connoted by these classifications, suggested to the writer the desirability of applying to the aggregate appraisals such measures of accuracy as might be obtained through statistical method. It was anticipated that in this way, an objective demonstration, however crude, of the accuracy of the assessment method might be obtained and points of technique requiring either improvement or elucidation before proof of the validity of the method would be possible, clearly indicated.

Accordingly in July 1932, the author prepared most of the following simple statistical analysis of the age data on the Reserve collection. The attempt was made never to carry the statistical treatment beyond the degree justified by the nature of the data.

There were available the stated and skeletal ages of 1540 cadavera. For 937 of these, an estimated age also was recorded. Two thirds of the series and two thirds of the males were whites. The Negro females nearly equalled in number the white females. For the entire series and for the white males the number of skeletons in each age group between 20 and 80 years may be considered adequate. The Negro males between 50 and 80 are not as numerous as would be desirable, but the series is representative. The bulk of the white males fall between 30 and 80 years with the greatest number in the fifth and sixth decades, while the majority of Negro males fall within the smaller range of between 20 and 50 years, with the greatest number in the third and fourth decades. The number of females is small at all ages for both stocks and the respective male series are deficient in numbers at ages above 80.

This series of 1540 skeletons carries through the cadaver laboratory file register to No. 1939 and includes all subjects for whom a skeletal age had been assessed at the time this study was made.

The number of individuals in which the skeletal age differed positively from the stated age was determined for the whole series and for a number of selected groups within the series, the latter groups including all that might conceivably shed light upon the objective of the study. The percentages of difference of skeletal and stated age shown by these several groups were then compared and their significance appraised.

Throughout all phases of the analysis the skeletal age was used as the standard of comparison because it is the most readily sustained scientifically and the remains are always available for critical re-examination. Differences were expressed as years by which the stated age was greater or less than the skeletal age.

The results of the various comparisons made are summarized in tables 4 and 5.

TABLE 4

Agreement of stated with skeletal ages

	No	%	
1. Total records with skeletal and stated ages	1540	100 0	
2. Skeletal age in agreement with stated	1116	72 5	
3. Skeletal age varies from stated but stated may be correct .	57	3 7	
4. Stated age not disproved by skeletal (items 2 & 3)	1173	76 2	
5. Total skeletal ages varying from stated (item 1 minus item 2) .	424	27 5	
6. Skeletal ages varying positively from stated (item 5 minus item 3, or, item 1 minus item 5)	367	23.8	
7. Stated age not disproved by skeletal, 1st 500 cad.	372	74 4	
8. Stated age not disproved by skeletal, 2nd 500 cad.	378	75 2	
9 Stated age not disproved by skeletal, 3rd 500 cad.	347	69.4	
10. Stated age not disproved by skeletal, 40 remain, cad	21	52.5	
Av .	365	73 0	
11. Stated age confirmed by hospital or other record	476	30.9	
			%
12. Total records with estimated ages	937	60.8	100.0
13 Estimated age coincides with skeletal	113		12.1
14. Estimated age within 5 years I of skeletal	566		60 4
15. Estimated age within 8 years I of skeletal	737		78.9
16 Estimated age within 7 years I of skeletal	686		73.1
17. Stated ages undoubtedly guesses	285		100.0
18. Undoubted guesses not disproved by skeletal age	184		64.6
19. Stated ages undoubtedly guesses but confirmed . . .	74		100.0
20 Undoubted but confirmed guesses not disproved	52		70.3

Variation between skeletal and stated age in selected groups

The groups established for comparison in respect to variation between skeletal and stated age fall into five categories: 1) general, the entire series; 2) groups representing progressively greater experience by the skeletal

assessor; 3) groups differing as to overt validity of the stated age; 4) white and Negro racial groups, according to sex; and 5) age groups by decades.

ENTIRE SERIES. Table 4 shows that in 1116, or 72.5 per cent, of the 1540 cases, the skeletal age was in agreement with the stated age. In 57 additional cases the bone age was assessed to be different from the stated age, but the possible correctness of the stated age was conceded, bringing

TABLE 5

Number of variations of stated from skeletal ages in selected groups of the series

No	Group	No in series	No. variations	% in agreement	% of variations
1	Entire series using item 5, Table 4	1540	424	72.5	27.5
2	Entire series using item 6, Table 4	1540	367	76.2	23.8
3	First 500 cadavera	500	128	74.4	25.6
4	Second 500 cadavera	500	124	75.2	24.8
5	Third 500 cadavera	500	153	69.4	29.6
6	Stated age "confirmed"	476	114	76.1	23.9
7	Stated ages undoubtedly guesses	285	101	64.6	35.4
8	Stated ages guesses, but "confirmed"	74	22	70.3	29.7
9	Male whites	.925	239	74.2	25.8
10	Female whites	117	24	79 5	20.5
11	Total whites	1042	263	74.8	25.2
12	Male Negroes	392	134	65.8	34.2
13	Female Negroes	106	28	73.6	26.4
14	Total Negroes	498	162	67.5	32.5
15	Ages 10–19	25	8	68.0	32.0
16	Ages 20–29	221	55	75.2	24.8
17	Ages 30–39	317	130	59.0	41.0
18	Ages 40–49	364	103	71.8	28.2
19	Ages 50–59	258	83	67.9	32.1
20	Ages 60–69	201	34	83.1	16.9
21	Ages 70–79	114	10	91.3	8.7
22	Ages 80–89	39	2	94.9	5.1

to a total of 1173, or 76.2 per cent, the number of cases in which the stated age could not be disproved by the skeletal. Oppositely phrased, *stated and skeletal ages were in passive agreement in slightly more than three fourths of the cases.*

This could mean either that the stated ages were substantially correct and the skeletal assessment, itself satisfactorily accurate, merely served as confirmation in the majority of cases, or, that the skeletal assessment technique was not sufficiently refined to reveal the degree of error inherent in the stated ages.

The lustral peaks of the curve of the stated ages and the circumstantial evidence on many of the death certificate ages specifically indicated that significant error is embodied in the stated ages, as previously mentioned. Hence the comparison just made indicates that *the skeletal assessment technique is not adequate to smooth the curve of the stated ages of the entire series* (fig. 1).

INCREASING EXPERIENCE OF THE SKELETAL ASSESSOR. Because so large a number as 1540 records were available and the skeletal assessment technique was being developed over a considerable period of time, the possibility should be examined, that the last skeletal estimates might be more accurate than the first. Accordingly, the first 1540 were divided into three groups of 500 each, according to time of receipt of the cadaver. The last of the first 500 was received, November 31, 1918; the last of the second 500, November 28, 1924; and the last of the third 500, January 18, 1929 Although the date on which a cadaver was received does not show when its skeleton was assessed, the dates of receipt must be used here because the skeletal assessment cards are undated. In general a skeleton was assessed the same year as macerated, which was about a year after the cadaver was received.

On this basis, it appears reasonable to infer that our first group of 500 skeletons ages represents about five years' experience in assessing, and the second and third groups of 500 embody the results of about five years' additional experience each. If the assessment technique improved progressively, the percentage of cases in which the stated age is challenged by the skeletal, should rise as we pass from the first group to the third.

Table 4, item 7, 8, 9, shows that this does not occur. In the first 500 cases, the stated ages of 372, or 74.4 per cent, are not disproved by the skeletal; in the second 500, the number not so disproved is 376, or 75.2 per cent, and in the third 500, the number passively agreed to is 347, or 69.4 per cent. The average for the three series being 365 or 73.0 per cent.

Since the agreement in the last 500 is smaller than in the first two groups, it might be that a trend toward greater precision in skeletal age definition had begun, but there is no justification for saying more than that *improvement of assessment technique with increasing experience as measured by increasing challenge of the stated age is but slightly apparent in the series.*

VARIATION IN VALIDITY OF STATED AGE. Another possibility which suggests itself as indirect evidence on the accuracy of the skeletal age is the amount of agreement with stated age in groups in which the accuracy of the age record is known to be different.

The ages of 476 of the 1540 cadavera, 30.9 per cent, have been "confirmed" by the hospital or institutional record where the individual was confined prior to death. This means that generally, but not always, the

subject made a statement of his own age before death. It does not presume that such persons knew or stated their ages correctly. Certainly the inference is justifiable, that this series embodies a degree of confirmation of the ages which cannot be ascribed to the entire series.

The skeletal age was in agreement with the stated age in this series of 476 "confirmed" ages in 362 or 76.1 per cent, of the cases. If the "confirmed" ages series is more correct than the whole, a higher percentage of agreement between skeletal and stated ages would be anticipated in the former. This expectation is realized only in part, for the agreement is 3.6 per cent higher than in the 1095 cases, 72.5 per cent of the entire series in which no disagreement is expressed, yet it is actually 0.1 per cent less than the agreement of 76.2 per cent obtained when there are added to the 1095, the 57 cases in which a skeletal age different from the stated is assigned but it is admitted that the stated age may be correct.

It must be recognized that the "confirmation" of the ages has not very appreciably increased their accuracy as determined by the comparisons made here, and although some increased validity has undoubtedly been obtained, this could have affected only approximately 57 cases.

No additional light on the accuracy of the skeletal age appraisals has been afforded by this comparison.

Selecting a group of the opposite nature, a series of 285 cases was obtained, in which the data on the death certificates indicated that the stated ages were undoubtedly guesses. Here the skeletal and stated ages were in agreement in only 184 or 64.6 per cent of the cases.

This is the lowest percentage of agreement encountered in any of the comparisons yet made. *It definitely suggests that the "guess" series incorporates more error than the "confirmed" series*, showing 11.5 per cent more disagreement than the latter. It does not contribute new light on the accuracy of the skeletal appraisal beyond implication that the latter is somewhat better than a guess.

The difficulty of establishing authenticity for the stated age becomes peculiarly apparent from an additional small series. Of the series of 285 stated ages which were undoubtedly guesses, there were 74 which had been "confirmed" and so were included in the series of 476 "confirmed" ages. These "confirmed guesses" were mostly individuals found either unconscious or under circumstances which did not yield any information about them, hence, the entry on the hospital or institutional record and which constituted the confirmation, was itself a guess.

In this series of 74, the stated and skeletal ages were in concurrence in 52 individuals, 70.3 per cent. This intermediate percentage has a neutral value in respect to the object of our comparisons. It affords some rein-

forcement to the view later developed, that *the skeletal age and a good guess are of about the same order of accuracy.*

RACIAL GROUPS. Table 5 shows that there was greater agreement between stated and skeletal ages in the 1042 whites (799 cases of 74.8 per cent), than in the 498 Negroes (336 cases of 67. 5 per cent), a difference in concurrence of 7.3 per cent.

Taken by sex, the males differ most. There was agreement in 686 of 925 white males, 74.2 per cent, and in 258 of 392 Negro males, 65.8 per cent, there being 8.4 per cent less agreement in the Negro than in the white male series. In the females, the total number of which is small for both races, agreement was relatively high for each. Concurrence in 93 of 117 white females, 79.5 per cent, was the highest of any racial grouping, and in 78 of 106 Negro females, 73.6 per cent, slightly above the average for the entire series.

In this series *discrepancies between skeletal and stated ages occurred most frequently in the case of the Negro male.* There is nothing in the data to suggest the cause of this difference.

AGE GROUPS. The percentage of agreement between the two age statements shown by the age groups in table 5 has certain significant features The second, fourth and sixth decades show less agreement than the average; the third, fifth and seventh decades approximate the average agreement; and the eighth and ninth decades present extraordinarily high concurrence.

The 8 dissenters among the small number of 25 individuals of both races and sexes in the second decade are mostly Negroes though the percentage is about the same for the 3 white males. A greater and more reliable disagreement with the stated age would be expected here because better age standards are available. On the other hand, a more dependable stated age would be looked for in these young subjects The group is too small to justify conclusions, however.

In the fourth decade, the small proportion of agreement, 187 out of 317 cases, 59 per cent, the smallest of any of the selected groups of table 5, is due to the Negro component of this age group. Barely half the males, 54, 50.5 per cent of 109, and less than half the females, 14, 46.2 per cent of 26, showed concurrence of stated and skeletal ages. Without doubt this high discrepancy in these Negro estimates must be due to some special factors not inherent in the numbers involved. The data do not show whether these factors lie in unusual error in the stated ages or inapplicability of the age determinators used or both.

The disagreement in the Negro male series is high also in the fifth decade but this is concealed in the total percentage by the much greater num-

bers of the white male series in which the discord approaches the general average.

In the sixth decade the percentage of non-concurrence is again relatively high but here it is due to the male whites.

Although the number of male whites is significantly large in the seventh and eighth decades, the percentage of disagreement is surprisingly small.

In fact, perhaps the most striking feature about the age groups is *the high percentage of agreement between stated and skeletal ages in all the series after age 60.* This implies not a greater correctness in the stated ages of the elderly but a greater inability of the skeletal age to dispute the death certificate statement.

It may be noted that *the largest percentages of disagreement for both stocks occur in those age groups presenting large but not the largest numbers of individuals.* These are the fourth and fifth decades for the Negro and fifth and sixth for the white. *The ages between 30 and 60 are those in which the greatest discrepancy occurs.*

Differences in variation according to race and sex

Table 6 presents the average deviations of 425 cases in which the skeletal age differed from the stated age, according to sex and race. The average deviation for this entire series is practically 10 years. *The deviation of 12 years in the Negro is greater than that of 9 years for the white.* The skeletal age does not vary from the stated in a large percentage of cases but it does when the variation tends to be of considerable degree.

This reinforces the impression reported above that the skeletal age determinators do not permit the bone age estimate to vary conclusively from the stated age unless the difference between the two statements is marked.

Examination of *the average deviations of the several age groups reveals a consistent increase, with one exception, moving from the younger to the older ages.* For the decades with the greatest number of individuals, the fourth, fifth and sixth, the deviation is about 8 years. The third, seventh and eighth decades also have representative numbers, and their respective deviations of 5, 10 and 18 years, leave no doubt as to the reality of the increase in amount of deviation with increase in years (table 6).

When the facts that the seventh, eighth and ninth decades show 1) both the highest percentage of agreement of any age groups between stated and skeletal ages and 2) the highest average deviations in those cases in which the ages differ, are considered together, it follows that *above 60 years, the skeletal determinations are less conclusive than at younger ages, since in these elders the skeletal age disputes the stated less frequently and when it does so, the degree of variance is greater.*

The interpretation of the average deviations must be cautious because the numbers of females whose stated ages varied from the skeletal in any

age groups of both stocks must be considered inadequate and for the males only the fourth, fifth, sixth and seventh decades may be held to show significant numbers in the whites, and the third, fourth and fifth decades in the Negro. The average deviation of the variations of the males of these specific age groups for the whites is 9.3 years and for the Negro 8.1 years. *Thus when series size is taken into account, the deviation for the white is greater than that for the Negro.*

If to the decades just cited are added the eighth decade for the white males and the sixth decade for the Negro males, we have the age groups showing the most representative numbers in the general series.

The eighth decade in the white males and the sixth decade in the Negro males, both show a relative decrease in the percentage of cases in which

TABLE 6

Average deviations in years of variations of stated from skeletal age

Age	MW	FW	TW	MN	FN	TN	Total
10–19	5 0	—	5.0	3.4	2.5	2.9	3.6
20–29	6.6	4 2	5.4	4.3	4.2	4 2	4.8
30–39	9.3	6.8	8.0	8 5	9.7	9 1	8.6
40–49	6.1	11.7	8 8	11.5	5 5	8 5	8 7
50–59	12.0	—	12 0	9 4	10 0	9.7	10 8
60–69	9.8	7.0	8.4	15.0	—	15.0	10 6
70–79	13.0	16.0	14 5	26.0	17 0	21.0	18 0
80–89	10.0	—	10.0	25.0	—	25 0	17.5
Total	9 0	9 1	9.0	12 9	8 1	11.9	9 9

skeletal and stated ages disagree and an increase in the average deviation of the dissents recorded. This may be regarded as elaboration of the conclusion above that *with advancing years* (above 60 in the first statement), *the precise definition of age by skeletal determinators becomes more difficult.*

Since age decades 3, 4, 5, 6, 7 and 8 in the white males and decades 3, 4, 5 and 6 in the Negro males comprise the whole of the representative age groups of the series, these may be examined as a unit as a check on the conclusions derived from the other age-race comparisons. This check showed only one point of difference from the latter. The Negro exhibits a smaller average deviation than the white.

Analysis of distribution in number of years, by sign, of the 425 cases in which stated and skeletal ages differed showed that although the range of variation is from 1 to 37 years, 381 or 90 per cent of the variations are between 1 and 15 years, with the mode at 10 years. Our average deviation of 10 years for the series thus appears fairly representative. It would probably be justifiable and do greater justice to the skeletal assessment tech-

nique to consider that *9 years is the average deviation of skeletal from stated age shown by this series.*

This is equivalent to saying that *the skeletal assessment technique as shown by these data can probably approximate the true age of an individual within plus or minus nine years.* As to age groups the skeletal assessment may come, between ages 10 and 19 years, within three and a half years;[1] between ages 20 and 29 within five years; between ages 30 and 49 within eight and a half years; between ages 50 and 69 within ten and a half years; and above 70 within eighteen years.

The distribution of the variations of stated age from skeletal age in number of years by sign yields interesting evidence on the subjective element in the skeletal assessment.

Of the 425 variations, the stated age was greater than the skeletal in 203 cases and less in 223, suggesting a slight tendency for the stated age to be less than the real age as indicated by the bones. This "minus" skewness obtains for the male and female whites and the female Negroes. In the male Negroes the stated age was greater than the skeletal in somewhat more than half the cases. *There appear no grounds for attaching special significance to the slight negative bias of the series of variations as a whole.*

The tendency for the skeletal age to be assessed older than the stated age in male whites and younger in male Negroes is most marked in the 103 cases in which the two ages differed by 10 years.

These 103 cases of variations of ten years plus or minus constitute the most significant feature of the table. The only interpretation this mode permits is that *the assessor had a definite tendency, manifest in nearly a fourth (24.1 per cent) of the cases, to assign a skeletal age ten years greater or less than the stated age.*

At variations of five years, fifteen years and twenty years there are peaks in the frequency polygon of the deviations. These, considered with the ten year mode, suggest *the same tendency to concentrate in lustra of five years when disputing the stated age, as was apparent in the frequency distribution of the stated ages themselves.*

There are no other arresting features in the table of distribution of variations in the age estimates. The conclusion appears warranted that *the subjective element is apparent in the skeletal age estimates in the mode at 10 years and peaks at 5 years lustra in the frequency distribution of the variations.*

The series of estimated ages

The frequency distribution by year according to sex and race of the 937 age estimates made on inspection of the intact cadaver was plotted. The

[1] Reliable standards otherwise available for this age period render this figure of no value.

racial and sex composition of this group is similar to that of the entire series, with a slightly larger proportion of Negroes of both sexes. The value of this series lies in the fact that it is definitely known that all these ages are guesses by one observer.

The frequency polygon shows graphically the remarkable concentration of the estimates in years which are multiplies of five. Seven hundred sixty-three or 81.4 per cent of the total of 937 estimates of age 60 or older, only 5, 2.3 per cent, are not a multiple of five. It might be said that for this period no attempt was made to express the age otherwise, implying the belief on the part of the appraiser that he had not even a subjective basis for a closer appraisal. Of 592 estimates of 30 to 59 years, only 98, 16 5 per cent, are not multiples of five. Eighty of this 98 are in terms of the "3" above lustra ending in zero and the "7" above those ending in five, as 23, and 27. These are the intermediate points between the five year multiples and form secondary peaks in the frequency polygon. Exactly half of 122 estimates from age 20 to 29 are not of the five year multiples, 20 to 25 years, but here again the secondary concentration in the intermediate age is apparent. The ten estimates of less than 20 years are evenly spread betwee ages 17, 18 and 19.

It is unmistakably clear that *the appraiser consciously attempted to estimate the age in terms of the nearest multiple of five or the intermediate point between two such multiples.* This obtains for every age from 17 to 85 inclusive. At no age does there appear any concentration in the integers next to five year multiples as *29* or *31*. It appears justifiable to infer that these estimates represent an appraisal of age within what the observer thought was the nearest five years. In 15 per cent of the cases an attempt was made to come within the nearest two and a half years, such cases diminishing in number above 30 years. Only below age 30 is any attempt apparent to assess an age not a multiple of five or the intermediate between two such multiples.

The lustra and intermediate peaks of the curve of estimated age must be interpreted as the result of the considered opinion of the observer that the regular attempt at more specific estimates was not justifiable.

With reference to variations of the estimated age from the skeletal age, we note that there are 824 such variations. The two ages were in agreement in only 113 or 12.1 per cent of the cases. In comparison with the 72.5 per cent of cases in which skeletal and stated ages are in practical agreement this appears quite small. But it must be remembered that the two ages here must agree exactly. In the case of the skeletal and stated ages agreement means merely that the skeletal is not able to disprove the stated age. If we broaden our base in the comparison of estimated and skeletal ages, we find that 566 cases of 60.4 per cent vary five years or less from the

skeletal age, 686 or 73.1 per cent vary seven years or less, and 737, or 78.9 vary eight years or less.

Thus *the frankly guessed ages which do not vary from the skeletal age by more than seven years, include as large a proportion of the estimated ages, as the number of cases in which the skeletal age cannot disprove the stated age, forms of the entire series.*

The skeletal age thus disputes the estimated age more frequently than the stated age. Since the cases in which the estimated age does not differ by more than seven years from the skeletal includes approximately three-fourths of the whole, and since the skeletal will not dispute the stated age in approximately the same percentage of cases, *the skeletal assessment technique cannot purport to approximate the true age by more than seven years,* for the adult period as a whole, recognizing as we do, that the series of stated ages represents a greater body of truth than does the series of estimated ages.

The conclusion is thus indicated that objective proof of the validity of the skeletal ages assigned these 1540 specimens cannot be obtained, but indirect evidence connotes that the assessor did not manifest a confidence in it greater than is warranted by the statement that *the skeletal assessment technique may approximate the true age within seven years, for the entire adult span, somewhat more closely in the earlier years and with greater latitide in the later.* Such comparisons as it has been possible to make with the series of skeletal stated and estimated ages tend to support this impression.

It appears obvious also from comparison of the frequency polygons of the stated ages and the estimated ages, that the stated ages present a more even distribution than does a set of patterned guesses, and therefore might be presumed to embody a greater proportion of truth than the latter, an assumption which might be made on a historical basis also.

Summary of Analysis of Age Estimates

1. In the entire series, stated and skeletal ages are in passive agreemnt in more than three fourths of the cases.

2. The skeletal assessment technique is not adequate to smooth the curve of the stated ages of the entire series, which shows peaks at each five year lustrum.

3. Improvement of the assessment technique with increasing experience, as measured by increasing challenge of the stated age, is but slightly apparent in this series.

4. Since a sub-series of skeletons whose stated ages had been 'confirmed' by institutional records, presents approximately the same proportion of agreement between skeletal and stated ages as does the entire series, and since this sub-series may be presumed to embody more accuracy in the

stated ages than does the entire series, the fact that the skeletal assessment technique is not a tool sufficiently refined to reveal inaccuracies in the stated ages by smoothing their curve, is again revealed.

5. A sub-series of cases in which the stated ages were undoubtedly guesses, presents 11.5 per cent more disagreement than the series of "confirmed" ages, which suggests that the skeletal estimate is better than some of these guesses.

6. A sub-series of "confirmed" guesses suggests that the skeletal age estimate and a good guess based on the intact subject or cadaver, are of about the same order of accuracy.

7. There was significantly (8.4 per cent) less agreement between skeletal and stated ages in Negro males than in white males or the small female series of both races. In the Negro males and the series in which the stated ages were undoubtedly guesses, the agreement was about the same (65 per cent). Nothing in the data would suggest the cause of the difference in the case of the Negro male.

8. In respect to age groups, the second, fourth and sixth decades show less agreement than the average for the entire series; the third, fifth and seventh decades approximate the average agreement; and the eighth and ninth decades show very high concurrence.

9. The ages between 30 and 60 are those in which the greatest discrepancy occurs.

10. The largest percentages of disagreement in both stocks occur in those age groups presenting large, but not the largest, number of individuals. These are the fourth and fifth decades for the Negro, and the fifth and sixth for the white.

11. The high percentage of agreement after age 60 is the most striking feature of the age groups. This implies not a greater correctness in the stated ages of the elderly, but a greater inability of the skeletal appraisement to dispute them.

12. In the approximate fourth of the series in which the skeletal age differed from the stated age, the average deviation was practically 10 years.

13. The deviation of 12 years in the Negro is greater than that of 9 years for the white.

14. The average deviations of the several age groups show a progressive increase moving from the younger to the older ages.

15. Above age 60, the skeletal determinators are less conclusive than at younger ages, since in these elders the skeletal age disputes the stated less frequently and when it does so the degree of variance is greater.

16. When series size is taken into account, the deviation for the white (9.3 years) is greater than that for the Negro.

17. Age decades 3, 4, 5, 6, 7 and 8 of the white males, and decades 3, 4, 5 and 6 of the Negro males comprise the age groups of the series with representative numbers.

18. This analysis indicates that the skeletal assessment technique can probably approximate the true age of an individual within plus or minus nine years.

19. Between 20 and 29 years, the skeletal assessment could appear able to approximate the true age within five years; between 30 and 49, within eight and a half years; between 50 and 69, within ten and a half years; and above 70 within eighteen years.

20. There was a slight tendency for the skeletal age to be assessed greater than the stated age, but there is no evidence that this skewness has particular significance.

21. The skeletal age tended to be greater than the stated in male whites and less in male Negroes.

22. The fact that a fourth of the deviations (24.1 per cent) were of 10 years greater or less than the stated indicates a definite tendency on the part of the examiner to assign a difference of this value.

23. The greater frequency of deviations of 5, 10, 15 and 20 years shows the same tendency to concentration in years which are multiples of five as is manifest in the frequency of the stated ages.

24. The mode of deviations at 10 years and their concentration in five lustra is evidence of the subjective element in the assessment technique.

25. In the estimated ages the appraiser consciously attempted to estimate the age in terms of the nearest multiple of 5 or the intermediate point between two such multiples.

26. It is inferred that the observer believed that the regular attempt at closer approximations was unjustifiable.

27. The frankly guessed ages which do not vary from the skeletal age by more than seven years, include as large a proportion of the estimated ages as the number of cases in which the skeletal age cannot disprove the stated, forms of the entire series.

28. Objective proof of the validity of the skeletal ages cannot be obtained.

Cartilage

Cartilage is largely a tissue of the growth period, hence its age changes and likewise its pathology are best exemplified in early life. With these we have nothing to do in this volume though it should be noted that the record of its early infirmity may remain throughout life in malformations and deformations of bony structure. There do occur permanent relics of disturbance of cartilaginous structure dating from its ageing process in early

childhood. Such conditions are Schlatter's disease of the tibial spine; Kohler's disease of the navicular of the foot; subdivision of the navicular (scaphoid) of the hand; emarginate patella, split patella and accessary patellar ossicles; separate neural arch of the fifth lumbar vertebra. In the last mentioned there is a tendency to slipping forward of the fifth lumbar vertebra with its superimposed vertebral column upon the upper surface of the sacrum, a condition known as spondylolisthesis.

We do however see changes with age in cartilage during mature and advanced years and are mainly indebted for information on this subject to the researches of Amprino and Bairati (1–4). Hyaline cartilage, as exemplified in the trachea and costal cartilages (1), adds to its substance by the transformation of connective tissue fibrils from the perichondrium, a process which is at its height at about the twentieth year. Costal cartilage reaches maturity earlier than tracheal cartilage and therefore shows regressive features much earlier. Among these features is albuminoid transformation which develops between the tenth and the twenty-fourth year in both types of hyaline cartilage and remains constant thereafter throughout life. Fibrillar changes also are found in the costal cartilages. Calcification is said to take place at different ages and is always present by forty years. In roentgenoscopic examinations at Western Reserve it has been found widespread and far advanced in costal cartilages of medical students and cadavera by the twenty-second year. Roentgenographic and anatomical observations strongly suggest that if calcification does occur it is just as likely to take place in early adult life as later. Actual bony transformation is said to occur in the tracheal cartilages in about 22 per cent of bodies over forty years of age.

Among the most striking of age changes is the appearance of secondary new formations of cartilage developed from perichondrium in the trachea of bodies over forty years of age and within the fibrillar areas of costal cartilages. Thus cartilage is one of those tissues which maintains till late in life a mechanism for the renewal of youth. New formation progresses side by side with regressive changes but it must not be assumed that this power of renewal is at all vigorous (91).

Histological details of the fibrillar transformation of hyaline cartilage as seen in the costal cartilages of the rat have been well described by Dawson and Spark (21). A change in density occurs in the matrix with unmasking of fibrillae particularly in the axial region. Small scattered globules of fat and glycogen appear in the cells whose protoplasm is reticulated and stains lightly. Surrounding this now differentiated axial core is an intermediate zone of which the cells show a dense and homogeneous cytoplasm, with a lightly staining nucleus, a few large fat globules and a peripheral row of granules in vacuoles. The subperichondrial zone exhibits smaller cells

without granules or globules. Next there appear clefts in the intermediate zone produced by local resorption of matrix in the region of atypical cells. A definite architectural pattern is developed in the disposition of these areas of resorption and in the fibrillae which cross the clefts. Modifications of the fibrillar systems rapidly follow resulting in a secondary fibrillar pattern which spreads eventually to the subperichondrial zone but not so distinctly into the axial zone. Occasionally, and particularly in older animales, the subperichondrial zone shows resorption of matrix and the cartilage cells freed from their matrix lie along the fibrils like fibroblasts. Vascular invasions, irruptions of active fibroblasts and even scanty ossification occur. All these features are deeply instructive, not only from the point of view of age changes, but also from the analogy they show to the stages in bone formation in those areas of the skeleton where local organizers determine the development of that tissue.

Elastic cartilage was studied by Amprino and Bairati (2) in the ear and epiglottis. It undergoes the same changes as hyaline cartilage though not to the same extent. Elastic fibers increase in number throughout life and may even form sheets but as the number increases the elastic quality diminishes.

For examples of fibrous cartilage Amprino and Bairati (3) chose the intervertebral disc between second and third lumbar vertebrae and also the cartilage of the symphysis pubis: of the two, the cartilage of the symphysis, in mature years, is nearer hyaline cartilage in its structural characters.

By the age of twenty years intervertebral cartilage has reached full maturity of structure. This is attained in the symphysial cartilage at thirty years. Thence to about sixty years is the period of mature life. Regressive changes are thereafter predominant. These changes are penetration by connective tissue and blood vessels, degeneration, calcification, necrosis, lacerations and hemorrhages. Already at about thirty years a fibrous change invades the hitherto hyaline cartilage of intervertebral and symphysial areas beginning at the periphery and reaching the central portion by about sixty years. Changes in the cartilage are closely related to synchronous changes in adjacent bony surfaces. The textural changes on the symphysial face of the pubic bone have already been described (see pp. 800–803) as a typical example. The transformation of hyaline into fibrous cartilage is thus one of the earliest signs of ageing in the body (80). The degree of this change can be approximately estimated by plunging a knife blade into the disc close to the body of the vertebra where the fibrosis first appears and noting the resistance encountered. With the onset of calcification the difficulty of inserting the knife is greatly increased: a second attempt nearer the midvertical point of the disc may be necessary

or the procedure may even have to be abondoned. Starting at about ten years in the intervertebral disc and about fifteen years in the symphysis, the number of cells enclosed within a single capsule increases but this change commences in the depth and reaches the periphery at about forty years. Fibrous cartilage undergoes less natural retrogressive change than either hyaline or elastic cartilage but its power of repair is likewise small. Perhaps the greatly altered function of the vertebral column in man, when contrasted with other mammals, predisposes the intervertebral discs to a regressive modification of the normal ageing process. Being cartilaginous structures however they tend to show degenerative processes at a comparatively early age in lower mammals as well as in man (77–83).

For an adequate description of the life history of that very complex structure, the intervertebral disc, the account by Beadle (8) should be consulted. I have made no mention of chorda cells of the nucleus pulposus for these have already disappeared before the adult or second period is reached (89). There is some doubt as to whether the cavity which appears both in discs and symphysis during childhood is a genuine joint cavity.

The nucleus pulposus is a glistening, white, translucent cushion of fluid consistency forming the central part of the intervertebral disc, exceedingly firm and elastic and probably under considerable internal pressure from its own turgor. Enclosing the nucleus and forming the peripheral portion of the disc is the annulus fibrosus studied as an example of fibrous cartilage by Amprino and Bairati (3). So densely fibrous is the annulus that one may have difficulty in identifying the cellular elements in a section examined with the microscope. The turgor of the nucleus pulposus depends on the fluid content of the tissue which gradually diminishes with age and may be completely lost in tissue degeneration. Puschel (55) gives the water content at birth as approximately 88 per cent for the nucleus and 78 per cent for the annulus. It diminishes rapidly during the first year and by the age of three years has attained a value of 76 to 78 per cent for the nucleus and 70 per cent for the annulus. Thereafter the annulus remains steady until old age when its water content sinks a little lower. The nucleus however steadily diminishes in its water content which gradually approaches that of the annulus so that, in a woman of seventy seven years, its water content was 67 per cent while the annulus had maintained a value of 69 per cent. Compared with those of age, individual differences in water content are small and probably constitutional in origin. In degenerated discs the water content depends on the type and degree of change. A swollen and moist appearance of the disc on section is the earliest sign of degeneration but such discs do not register any change in water content. The appearance must therefore be due to a modification in the constitution of the tissue. But the dry, crumbling and fissured disc, more advanced in

degeneration, shows a water content deviating in less or more degree from the normal.

A special though aberrant age change in cartilage so far recognized only in the publications of Todd and in those of Dawson (20, 67–68, 78–79, 84, 86–87) is that characteristic of cartilage which has remained at a site in the skeleton beyond the age when it usually disappears through transformation into or replacement by bone. This cartilage can be described as in a "lapsed" state for the reason that its occurrence in diaphysoepiphysial planes where union should have already been perfected between shaft and epiphysis. It also occurs however in sutures of the skull and in all persistent symphyses like that of the pubis. The hyaline cartilage of the plane becomes increasingly fibrous and sometimes cystic in places. A thin lamella of bone forms over both faces of the cartilage capping the adjacent bone ends with a wax-like texture and shutting off the cartilage from the cancellous tissue. Dawson has described the histological features very well (20). The condition is caused by any nutritional or other deficiency which retards the rate of skeletal maturation, It is observable in rachitic bones of young rats maintained for more than three weeks on a rachitogenic diet (90) where it is still a partially reversible phenomenon. It is evident also in the more profund deficiency caused by experimental endocrine disturbance (84) where the phenomenon is irreversible. Eventually osseous bridges may erratically unite the periphery of the adjacent bones but never the deeper parts as in regular epiphysial union.

In a sense this is cartilage undergoing regular age changes in an irregular manner. It is not frankly pathological but is a borderline phenomenon and is of course characteristically seen in the long and often permanently patent sutures of the human skull. In the equally permanent human symphysis pubis its characteristic of a structural pattern changing as age increases had already been fully described.

Bennett, Waine and Bauer (9) described in meticulous detail the changes with advance in years in the cartilages of the knee joint. These constitute a progressive pathologic process which they term "degenerative joint disease" present in every subject over 15 years. As early as the second decade the articular cartilage over the central portions of the tibial condyles and to lesser extent, the patellar surfaces of the femur, presented surface irregularities beneath which the matrix was swollen and fibrillated and occasionally fissured and cleft. Sections of the menisci showed slight fraying and splitting of the matrix accompanied by diminution in the number of cells. By the fourth decade slight roughening and striation is found on those portions of the cartilaginous tibial surfaces that articulated with the femoral condyles. Corresponding changes occur in the latter. This roughening, fraying and splitting of cartilage increases with advancing years. In

the fifth decade ulcerations are common. Later deep, sharply defined erosions and widespread thinning of cartilage appears. The end point of the process is complete denudation of the articular surfaces. The degree to which this occurs varies in individuals, even of extreme age.

Before leaving this subject some mention should be made of the vascular channels and their role in cartilage. Hurrell (29) has summarized the literature and added thereto his own investigations and critical analysis. In man the channels make their appearance in the third fetal month and it is only at a later stage that they are occupied by blood vessels. They are therefore primarily nutritive in character although when ossification of cartilage sets in, it is along the blood vessels in the course of these channels that the bony tissue is laid down. Linberg (43) has made a study of the life history of these channels which reach their full development in the rib cartilages by thirty years. They are present according to this author up to about sixty years when atrophy of the marrow elements is accompanied by the formation of smooth-walled spaces and then by the disorganization of the vascular channels. Henschen (26) has confirmed Linberg's work by his roentgenograms of rib cartilages. The blood vessels apparently remain present in advanced age unless the cartilage becomes ossified. It is claimed that vascular channels are developed in permanent cartilages in order to permit the persistence unaltered of masses of any size inasmuch as the vascular channels appear to form in response to the demand of the deeper cells for nutrition.

In summary, it is obvious that cartilage though pre-eminently a tissue of the growth period, showing great power of activity in the early years, nevertheless persists as a tissue of adult and of old age and in consequence illustrates very clearly the types of transformation which characterize successive phases in the life span.

The hyaline cartilage of the bones (including the cartilages of the sternum, the costal cartilages, epiphysial cartilage (27), cartilage of the diaphyso-epiphysial plane and articular cartilage) and the hyaline cartilage of the respiratory passages (including nose, trachea, bronchi, and most of those of the larynx), so closely related in their histological appearance, add to their substance by the transformation of fibers from their investiture of connective tissue. Where this transformation does not mean the development of bone, as in costal cartilages and trachea it reaches its height at about the twentieth year precisely like its counterpart in the subperiosteal bony growth. Indeed both fibrillar changes and calcification are common in costal cartilages though less so in the larynx early in the third decade and actual bony transformation can be seen in both skeletal and respiratory hyaline cartilages long before the age of forty years though perhaps more commonly after that age.

If cartilage is to remain relatively immune to these age changes, as in the ear, the auditory tube, epiglottis, corniculate and cuneiform cartilages, the apical and vocal processes of the arytenoid cartilages, it takes the form of elastic cartilage which becomes more fibrous with age changing in the structure and elasticity of its special tissue but showing no tendency to calcify or ossify with increasing age.

On the other side stands fibrocartilage comprising every intra-articular disc and meniscus, the labra of the articular rims, the intervertebral discs and the symphysis pubis. Here fibrous modification has occurred early but maturity of structure is attained as in hyaline cartilage at about the twentieth year. Fibrous transformation of a more vigorous type now begins to appear and intensifies its activity as the years pass with this exception that invasion of the symphysis is delayed for another decade. Doubtless this peculiarity is associated with the special sexual character of the symphysis (84). It is at the symphysis indeed that one can study most readily the correlated and synchronous age changes taking place in the chief types of skeletal tissue, namely, cartilage and bone.

The precise meaning and wider significance of age changes in hydration in the nucleus pulposus of the intervertebral discs, a process the progress of which is quantitatively measurable, are nevertheless still obscure.

The curious phenomenon of cartilage which has been retained in the skeleton beyond the date of its regular disappearance is seen in human cranial sutures and symphysis pubis. This "lapsed" form of cartilage presents precisely the pattern of transformation which one would expect, namely, increasing fibrous change with ultimate regressive modifications.

Conclusion

Available for the study of age changes in the skeleton are two documented collections comprising more than 4100 individuals in the anatomical laboratories of Western Reserve University in Cleveland and Washington University in St. Louis. The assemblage of these collections alone represents monumental achievement, for which investigators of skeletal ageing are indebted to the late Dr. T. Wingate Todd and Dr. Robert J. Terry respectively.

These combined collections constitute a unique material resource unrivalled by that available for the study of ageing in any other bodily system. The quantity of skeletal material available for the study of ageing phenomena is vastly increased when the large collections of skulls and skeletons of unattested age in the major museums of the country are considered in addition. The contents of these have been catalogued by the present writer (17).

Because of the great individual variability in the expression of age

changes in the skeleton, large quantities of material are particularly important for elucidation of the morphological facts.

The scientific potential of the Reserve and Washington collections for knowledge of skeletal ageing has been realized only in minor degree. Pioneer and exploratory studies with modern concepts have covered nearly every aspect of skeletal ageing. Comparative mammalian investigations of great value to the understanding of human phenomena have been made.

As useful and important as these studies have been, they were based on much less material than is now at hand and for many desiderata most of the features investigated need to be restudied on larger series and in the light of newer collateral knowledge.

In this chapter the principal data extant on ageing in the skeleton have been reviewed. The differences in the character of the population samples from which present ageing criteria for the preadult and for the adult skeleton are derived, has been emphasized. While the roentgenogram of those of known provenience has been the basis for much revised and increasingly satisfactory ageing standards on the preadult skeleton, the dry bones of the unknown destitute have been the material for standards for the more difficult adult period which have been essentially unrevised since the first modern-type studies were published.

Because the roentgenogram is the chief source of information on the skeleton of the living adult, the need for techniques to chart ageing through this medium is obvious. The referrability of standards based on cadaver populations to living groups requires determination.

In the study of the problems of ageing in the adult skeleton much difficulty and confusion has resulted in the past from premature attempts to link age changes with age in years. The patterns of ageing differentiation are one thing. Their association with time is another. Individual variation in the progress of physiological and chronological ageing in the same person is still a third consideration. Strategic selection of problems for investigation will eventually permit the manifold pieces of the puzzle to be fitted together properly.

The physical labor, personal untidiness (one may get his coat soiled quickly examining many skeletons) and travel from place to place involved in the study of large series of skeletons may have diminished the attractiveness of such study to gifted workers. In addition, the work is very time consuming. Possibly it may be possible to accomplish with teams of workers what has not yet accrued from the efforts of individuals or pairs.

The fact that morphology today is in the shadow of radioactive tracers cannot obscure the fact that much information is yet to be gained from descriptive morphological studies of ageing in the skeleton, nor that an abundance of material is available.

The importance has been stressed of viewing the ageing of the adult skeleton in the perspective of the entire life span. The significance of nutritional, endocrine and genetic factors in influencing preadult skeletal development has been promisingly demonstrated. The valid identification of such influences in the adult should eventually be possible. This has already been shown in the case of variations in mineralization of the bones of the same person.

The ageing phenomena offer many possibilities for experimental approaches to problems presented by morphological findings in statistical series. Coordinated programs involving morphological, experimental and clinical approaches *should make an appearance in the near future.*

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SURGICAL PROBLEMS IN THE AGED

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Surgical problems in the aged differ from similar problems in younger adults rather in degree than in kind. Regardless of the age of the patient, the basic objective is rapid and complete rehabilitation following either accidental injury or surgical operation. Accidental trauma has been and will probably always be with us. Recovery from injury in the aged is similar to that in the young adult but differs only in details To be sure, older individuals are more likely to have certain types of injury, particularly those involving fractures of the neck of the humerus or femur, because of the bone atrophy which progresses with advancing years. But the treatment is basically like that used in younger individuals

A surgical operation always presents a problem in so far as the procedure is one of choice. In making a decision, one must compare the risk of the operation including anesthesia with the risk of not operating In the older patient, this decision must take into account the question of expectancy of life as well as the degree of suffering and disability already present and the likelihood of its relief by operation. A surgical operation is primarily designed to save or prolong life but may also be indicated as a means of minimizing or eliminating disability or pain even though it cannot prolong life. These questions are especially important in the patient with cancer, which is a frequent indication for operation in the older patient. In general, however, these problems resemble those in younger individuals except that the greater expectancy of life in the latter group justifies greater risks in order to correct severe disability. This is discussed in detail below.

The age of the individual, as has been emphasized throughout this text, should not be estimated solely in terms of his chronological age inasmuch as the physiological changes with advancing years do not occur at the same rate in all individuals. There are many who are more youthful at

the age of 80 than others at the age of 60. In estimating the expectancy of life as well as the risk of operation, it is the physiological age which must be considered rather than the chronological. This, indeed, fits most clinical experience. The physiological age is estimated in terms of the patient's behavior, mental and physical, the suppleness of his skin and the resiliency of his arteries. The body weight of the individual must also be considered, e.g., other things being equal, the obese patient of 60 is a much greater surgical risk than a thin patient much older. On the other hand, the existence of a long standing malnutritional deficiency in itself adds years to the chronological age.

In outlining the surgical problems in the aged, it is of value to discuss first the physiological changes which occur with advancing years as they influence the reaction of the individual to injury and his ability to withstand the effects of injury, particularly when carried out as an elective surgical operation. These changes have been discussed in other parts of this text, but they will be mentioned again here in their special context. They refer to the problems of wound healing, infection, cardiovascular stress, hepatic and renal function, central nervous system function, nutritional status and the systemic effects of injury ("alarm reaction"). Each will be discussed separately under the heading of General Considerations.

General Considerations

Historical survey

Surgeons have always had a traditional reluctance to operate on the aged. In the older textbooks a rising incidence of fatalities has been recorded in almost direct proportion to increasing age. Indeed, an operation of choice was considered too hazardous in most older individuals even when life was threatened by the disease which the operation was designed to cure. This attitude was perhaps justified in the early days of surgery, particularly before the development of asepsis and anesthesia, the two great advances which started in the latter part of the nineteenth century. With the twentieth century has come a steady increase in the safety of surgical procedures, and this has not only been due to progressive improvements in anesthesia, but to a deeper understanding and realization of the metabolic changes induced by operation. Even more important has been the knowledge which permits recognition and correction of certain nutritional deficits existing in patients requiring the various surgical procedures. The development of a scientific program for preoperative and postoperative care has enabled surgeons to carry out much more serious and much longer operations with a greater degree of safety than ever before. This advance has reflected itself especially in an increase in the safety of operations upon individuals of advanced years. Inadequate preoperative preparation and

postoperative care, although inexcusable in any age group, are not apt to be so serious in younger patients because they are able to withstand greater damage. But the older patient group will reflect poor surgical care by an increased mortality. With modern methods as used at the present time, it is not uncommon for a patient to be successfully relieved of his strangulated hernia or to have a gastric resection even when he is in the seventh, eighth or even ninth decade of life. A successful prostatectomy has even been reported in a patient aged 110 years (5).

Among the many and excellent studies of surgery in the aged is that of Brooks (3), who analyzed experiences with nearly 300 patients operated upon at the age of 70 years or over. Of this group, 33 had abdominal operations of which 11 died, including 3 with inoperable carcinoma. Twenty had herniotomies, of which group only 1 died. This report had a great influence in indicating that operation even at advanced ages was not necessarily followed by a prohibitive mortality. Even in a large municipal hospital where the general and nutritional conditions of patients are quite poor, Carp (4) reported 109 major operations, carried out in patients between 71 and 80 years of age, with an operative mortality of 25.8 per cent. There were reported by the same surgeon 50 operations upon patients between 80 and 90 years with an operative mortality of 38.4 per cent.

Despite the increasing evidence that the risk of operation on older individuals is not forbidding, many surgeons are still reluctant to carry out operative procedures on older patients. It is not that the patient himself or his family refuses this treatment, but simply that many surgeons are themselves unprepared to take the responsibility and added care required to operate upon such a patient. For example, one finds many older individuals handicapped for perhaps ten or fifteen years with trusses, even though they have readily operable hernias which really should have been repaired.

Wound healing

There is a general belief that the power of healing diminishes with advancing age. This belief stems largely from the writings of DuNouy (7), whose inferences, however, were based entirely upon observations on the epithelialization of granulating wounds in 2 wounded soldiers aged 20 and aged 40. Analysis of this evidence reveals very little if any justification for the belief that healing is impaired in the aged. Entirely apart from the fact that DuNouy's inferences were based on inadequate clinical data, the conclusions he drew have little bearing upon problems of healing following most surgical operations. This is due to the fact that healing in nearly all cases in not a question of the growth of epithelium across a defect in the skin, but rather of the tensile strength of a sutured wound. The latter in

turn depends upon fibroplasia of connective tissue and not upon the growth of epithelium.

Experimental studies on the tensile strength of wounds have shown that the young growing animal exhibits more efficient and rapid fibroplasia than adult animals. Indeed, these studies of Howes (8) confirm the clinical experiences of most surgeons who have long observed that babies and young children heal more rapidly than older children and adults. Until recently, however, no experiments have been made on adults of increasing age. This has now been done by Dalton (6), who in rats has shown that the tensile strength of abdominal incisions in the young and in the aged animal is quite similar. This, too, is in accord with clinical experience, for most surgeons have found that abdominal and other incisions in individuals of advanced age heal quite as rapidly as do those in the younger individual.

It is true that impaired vascularity of tissues will interfere with fibroplasia and retard or even prevent normal healing and that arteriosclerotic or other vascular disease is more frequent in the aged. This applies, however, mostly to the lower and upper extremity, and indeed, it is a common experience that injuries or operations in these parts of the body do not heal as well in older individuals. This is particularly true of fractures. The most notable example is fracture of the neck of the femur in which the deficient blood supply in the older individual usually precludes any chance of healing at all. Indeed, it is because of the deficient blood supply that the bone itself becomes brittle and is much more likely to break. This accounts for the frequency with which such fractures occur in older individuals even with but slight trauma.

Healing in general is influenced by many factors which respect no age. These factors include protein and vitamin C deficiencies, mechanical factors such as coughing, vomiting or any other mechanical strain which may tend to separate the integrity of an abdominal incision. The incidence of these factors may, but does not necessarily increase with advancing age.

Infection

Infection has long been the great bugbear of accidental injury as well as of surgical operations. The resistance of the older individual to various infections is in general much lower than it is in the younger individual. This is especially true of peritonitis, which accounts for many mortalities in intraabdominal lesions in the older individual. This is also true of pneumonia in the aged, which has always been greatly feared by surgeons as a cause of death after operation.

The danger of infection was tremendously reduced when aseptic technic was generally adopted. More recently, the introduction of chemotherapy

has played an important additional part in preventing or curing many infections which follow accidental trauma or surgical procedures. These developments have had a definite influence in reducing the mortality following operation in the older individual. Newer methods of preventing pulmonary infections are also important.

Cardiovascular stress

The status of the patient's cardiovascular system is of tremendous importance to the surgeon. When impaired, it increases the hazard of surgical shock and of vascular accidents following operation.

The circulatory apparatus is certainly less resilient in advancing age. Its compensatory response to hemorrhage is less effective, and even a moderate fall of blood pressure is of more serious import. Moreover, in the older individual, a given degree of tissue trauma has a greater tendency to lead to circulatory impairment as compared with the younger individual. Advancing years undoubtedly increase the likelihood of thrombosis and embolism due to the fact that the blood vessels are more rigid, less resilient and tolerate poorly the slowing of blood flow which often precedes thrombosis, especially in the leg veins. Furthermore, the intimal thickening and narrowing of the arteries which is so common with advancing years produces a fall in the blood flow which in turn favors venous thrombosis. It is true also that vascular accidents, due to rupture of arteries especially in the brain, are more likely in the diseased vessels of older individuals. Thus the older individual tolerates poorly abrupt changes in blood pressure, both decreases as well as increases.

These fundamental cardiovascular hazards of advancing years, however, must be considered along with the therapeutic procedures discovered during the past few decades designed to combat these so-called natural tendencies. Thus the development of blood banks for blood replacement has reduced the hazard of hemorrhage. On the other hand, the ready availability of intravenous therapy has carried with it the danger of excessive infusions. The injection of too much fluid is tolerated more poorly by the older than by the younger individual. While we have means of protecting the aged patient against the hazards of low blood volume, the very remedies when used in excess may prove more harmful than if not used at all. These considerations emphasize again the need for exact therapeutic knowledge and its careful application in the surgical care of the older individual.

The use of heparin and dicumarol to decrease the coagulability of the blood as well as the use of early leg exercises and ambulation has greatly minimized the tendency toward thrombosis and thus has reduced much of the hazard associated with pulmonary embolism in older individuals. Indeed, it is of interest to point out that early ambulation and termination

of bed rest as a means of preventing pulmonary embolism after operation was first practiced almost as routine after operations on older individuals, particularly those in the eighth or ninth decade. Curiously enough, while this procedure was considered necessary in old individuals, it was thought to be too hazardous for younger patients! It was later shown to be valuable for younger individuals as well. Now leg exercises and early ambulation by early termination of bed rest are advocated by most surgeons for patients at all ages.

The systemic reaction to injury

Much has been learned about the non-specific systemic reactions to injury sometimes called the "alarm reaction" or the adrenopituitary reaction (11). This response usually takes the form of such clinical manifestations as fever, tachycardia, asthenia, sensorial depression, etc. A number of specific metabolic changes have also been observed such as retention of sodium and excretion of potassium, a disturbance in carbohydrate metabolism and an increased excretion of nitrogen. The two last named mechanisms are part of the so-called catabolic reaction following injury.

Surgeons have long noticed that older individuals in the absence of complications even after severe surgical procedures showed very few systemic symptoms as compared with younger individuals. In the older patients, the pulse rate remains relatively unchanged, fever is less likely, they show much less pain, apprehension, asthenia, and indeed often look as if they had had no operation at all. By contrast, the younger surgical patient will respond in a more sthenic way with an increased temperature, pulse rate and will look much sicker. This difference is probably due to a difference in the degree of the adrenopituitary response, which is known to be much more intense in younger than in older individuals. Part of the difference may also be due to psychogenic factors. While there is great individual variability, the tranquility of maturity and the emotional serenity and stoicism which often accompany advancing years might be expected to produce less concern with the approach of danger. Older individuals often realize that they have already spent most of their useful and enjoyable life and are therefore less fearful of death. This may explain why they are calmer and suffer less psychic trauma following injury than is the case of more youthful patients.

Regardless of the reason, however, it seems apparent that this kind of behavior on the part of older individuals may actually be an advantage rather than a disadvantage as far as surgical convalescence is concerned. It must be emphasized, however, that this is true only in the absence of complications. It is well known that older individuals withstand complications poorly due perhaps to this very absence of an intense systemic re-

action, which, indeed, has been called by some the "fighting spirit of youth".

Renal and hepatic function

Any injury or operation is known to produce a slight to moderate amount of renal impairment. This may be of reflex origin or may be a part of the adrenopituitary reaction. A decrease of renal function is manifested by oliguria and sometimes by anuria, which is particularly likely after extensive operations. There has long been the impression that renal function decreases with advancing years. A number of studies have been made of the function of the kidneys at varying age periods without detecting any significant difference, at least as measured by the ordinary methods of determining renal function (10).

Despite these observations, it is a rather common clinical observation that impairment in the function of the kidneys following operation is much more likely, particularly after a severe operation, in the older than in the younger individual. The harmful effect of operation on renal function with advancing years is probably greater under ether anesthesia and for this we have definite and convincing experimental evidence. MacNider (9) studied the effect of a two hour ether anesthesia on renal function in dogs of various ages by measuring the urinary output and the alkali reserve. Very little change was found in any animal up to 4 years of age. In the older dogs, however, i e., those over 4 years of age and up to 11 years and 7 months, there was always a fall in the alkali reserve even before the urinary excretion was affected. However, the urinary output after the first hour showed a definite fall and anuria was not uncommon. The phenolsulfonphthalein excretion also fell and the urine in these older animals frequently contained albumin and casts. Similar observations are needed in humans. Postoperative excretion of potassium is lower in older than in younger patients (2).

Hepatic function is perhaps almost as important as renal function in maintaining the normal vital function of the individual. Yet very little is known of the influence of advancing age upon hepatic function, particularly as influenced by operation. The role of nutritional intake, however, is important at all ages and the deleterious effect of protein deficiency must always be avoided. It is likely that these influences are probably accentuated in the older individual as compared with the younger individual.

Changes in the central nervous system

There is undoubtedly an increasing rigidity of blood vessel walls with advancing years and this perhaps may be the explanation of the interesting

experimental observations made many years ago by Weed and McKibben (12) on the effect of age upon the changes of the brain volume induced by intravenous injections. These workers carried out many studies on the size of the brain as revealed by direct observation after craniotomy. After the intravenous injection of hypo- and hypertonic salt solutions, they noted that the brains of older cats reacted much less violently than did younger animals. For example, the brain bulged into the craniotomy opening following intravenous injection of distilled water in young cats, but this response was absent or less pronounced in older animals. On the other hand, the shrinking of the brain which was very definite following intravenous injection of hypertonic solutions in younger animals was often less marked or absent in the older animals. The clinical implications of these striking observations are not evident at the present time.

Locomotor function

One of the striking changes which comes with advancing years is the gradual impairment of locomotor function as shown by the increased liability of bones, joints and muscles to become disabled. Not only is injury to bones more likely because of their brittleness and atrophy, but tendons and joints are similarly prone to loss or impairment of function. Even immobility leads to severe and often permanent joint disability. Thus the importance of maintaining voluntary movement of muscles and joints is far greater in older than in younger patients. Even a simple Colles fracture, if put up in complete fixation for several weeks, may result in a permanently fixed wrist and fingers, and other neuromuscular disability.

Nutritional status

An increasing amount of information is being gathered in regard to the nutritional changes associated with advancing years. There is at present little evidence that the basic metabolic process associated with the ingestion and digestion of food is significantly different in the older as compared with the younger individual. What evidence there is suggests that the need for protein and vitamins tends to increase with advancing age. At the same time, it is rather well known that increasing age tends to provoke changes in the nutritional habits or intake of the individual which in turn may themselves lead to one type of deficiency or another. For example, as dentition fails, the older individual limits himself to the ingestion of soft or even liquid foods. Unless he is instructed or told how to take well balanced soft or liquid food, or does so of his own volition, he is apt to eat only carbohydrate and fat with little protein. A favorite item of food is white bread and gravy. As a result, various types of nutritional deficiencies frequently follow, usually those associated with a restriction of protein

and vitamin intake. Another factor is the tendency of older individuals to lose interest in food, to fall prey to various food fads or to develop idiosyncrasies which in themselves may easily lead to various deficiencies. Here, too, the most important is protein, and there is some evidence that many older individuals, particularly those who lose a great deal of weight, seem to ingest a smaller and smaller amount of protein and develop a definite protein deficiency. Even in those individuals who have not lost weight, or who may even have become obese due to the ingestion of excessive calories, protein deficiency may nevertheless be present. Further studies seem indicated.

Resistance to cancer

Cancer becomes relatively more common (as compared with other diseases) with advancing age. Yet it is a curious paradox that its virulence tends to become less. This is true of many types of cancer, but particularly that of cancer of the breast, which is apt to be a rapidly growing tumor and much more likely to be fatal in younger than in older women. Indeed, in very old women cancer of the breast may almost be a mild or harmless lesion. Lesions subsequently demonstrated as carcinoma have been observed to remain almost quiescent for many years in these older women. This may also be true of other types of cancer. From the surgical point of view, this characteristic of cancer means that diagnosis, while difficult in the aged, may at any given stage of the disease permit more adequate excision and a more likely cure because distant metastases are less likely to be present.

The problem of operation for cancer in the aged, however, is always conditioned by the question of the expectancy of life. In making a decision as to the desirability of a radical surgical procedure for the removal of cancer, the risk of the procedure itself must always be weighed against the expectancy of life in the particular individual. This relationship may perhaps be expressed in an arbitrary series of calculations as follows.

If 100 patients suffering from, say carcinoma of the esophagus, will *live on the average of one year, dying of their disease, the total duration* of this group would be a hundred years. If their normal expectancy is five years and 75 per cent of them could be cured (i e., 25 per cent mortality), the desirability of operation would be obvious, for then the total duration of life would be four hundred years in this group. On the other hand, if instead of one year, similar patients with carcinoma of, say the prostate, lived four years without operation, a mortality rate of 25 per cent would mean that the total duration of life with or without operation would be the same, i.e., four hundred years, thus detracting from the indications for radical excision. In other words, surgery becomes more

indicated despite an increasing mortality the greater the expectancy of life in those who are cured by the procedure.

These considerations, however, cannot be made dogmatically, first because the expectancy, while statistically sound, may not necessarily apply to a particular patient. For example, individuals aged 80 have an average expectancy of about six years, but in this group there may be several hundred who will live over ten years. To a certain extent, it may be possible to predict which of these individuals will survive the longest. This is based upon an accurate estimation of the physiological status of the individual with special reference to the presence or absence of excessive adipose tissue. Thus a radical procedure involving the mortality of even 50 per cent may be justified in an individual aged 70 if his normal expectancy after removal of the lesion could be placed at ten or fifteen years as compared with a survival of say 3 years from the untreated tumor.

Another factor of great importance is the existence of severe disability produced by the cancer itself, as compared with the disability which sometimes necessarily follows the surgical procedure. Extensive resections or a colostomy may be justified even if a cure is impossible provided the symptoms produced by the tumor are sufficiently disabling. Indeed, palliative procedures are frequently justified for the relief of severe pain, progressive intestinal obstruction or for the removal of a foul, infected, sloughing ulcer even at considerable risk with no hope of cure.

The answer to the question of surgery in the presence of cancer, therefore, must be an individual one, based upon careful consideration of the several factors mentioned above to which, of course, must also be added the attitude and feeling of the patient himself as well as the choice of his family.

Special Therapy for Surgery in the Older Age Group

As already indicated, surgical problems can be greatly minimized in the older individual by paying more attention to the details of his surgical care. In this sense, surgery in the older individual tends to present the same problems as those in the younger individual. The details, however, are more important because mistakes are more serious in the older patient.

Preoperative care

While many young individuals in relatively poor condition may withstand extensive operations without risk, this is not true of the older individuals. It is therefore more important that older individuals be prepared adequately for surgical procedures. This, of course, is not always possible in accidental injury or emergency operations, but in procedures of choice the therapeutic opportunity is often unlimited. Most surgical diseases sel-

dom require emergency operation. The few which demand immediate operation and offer little opportunity or justification for prolonged preoperative care include gunshot wounds of the abdomen, severe uncontrolled bleeding from other lesions such as peptic ulcer, a perforation of the gastrointestinal tract, strangulated hernia, etc. It is among these patients that delay leads to the highest mortality in both the younger and the older group. On the other hand, many observations have shown that in the non-acute case the lowest mortality follows operations in which an adequate amount of time has been available for preoperative preparation.

Preoperative preparation concerns mostly the correction of nutritional deficits. These may be relatively simple, as for example a depletion of water and salt which has followed excessive sweating, vomiting or diarrhea, or other loss of gastrointestinal secretion which can be replaced by injecting the appropriate solution of water and electrolyte. In other cases, the deficit will be more chronic in nature and involve various proteins of the body-tissue proteins, plasma proteins and hemoglobin. The importance of restoring deficits in the red cell mass and the plasma proteins has been emphasized by many observers and particularly in a paper by Behng (1), who has actually shown by blood volume determination that replacement of such deficits, in the older patient particularly, leads to a much lower incidence of complications and enhances the ability to carry out much more extensive surgical procedures with much less risk.

Correction of nutritional deficits by purely dietary means must not be overlooked, and in many cases constitutes a very important and simple method of preoperative preparation. In so far as the gastrointestinal tract is intact, the use of concentrated nutritional drinks especially containing vitamins and proteins for as long a period as possible greatly decreases the risk of operation in older patients and makes complications fewer and less hazardous. If the parenteral route must be used for the correction of these deficits, it is important to realize the inflexibility or lack of resiliency of the vascular system in the older individual, thus emphasizing the need for the slow intravenous injection of fluids and meticulous avoidance of excessive injections in these patients.

Other preoperative means such as evacuation of obstructed contents and the chemotherapy of the gastrointestinal tract are all described in surgical texts and in manuals of pre- and postoperative care. The actual *details as well as the principles are the same in the older individual as in* the younger except that here too it is necessary to be much more meticulous particularly in avoiding excessive dosage than it is in the younger individual.

The barbiturates and narcotics must be used with great care in the older patient and large doses studiously avoided because of their dangerous de-

pressive action on the vital functions. Chloral hydrate is best used for sedation and demerol rather than morphine for analgesia.

The operation itself

The risk to the patient's life and the seriousness of the postoperative course depend to a large extent upon the operation itself, and here both the surgeon and the anesthetist are directly involved. Anesthesia is so important that it will be discussed in a separate chapter in the text. As far as the surgeon is concerned, the older individual is much more subject to the hazards of tissue trauma than the younger individual, and thus the surgeon has a greater responsibility to minimize as much as he can the damage due to the procedure itself. This calls for much more delicate surgical technic, eliminating unnecessary manipulation and trauma, minimizing extensive intraperitoneal exploration, avoiding unusual positions and severe traction, the use of careful hemostasis and of fine non-absorbable sutures rather than heavy catgut.

These factors are of course important in all patients, but they are emphasized here because the younger patient can overcome the effect of rough surgery much more easily than the older patient, and thus the hazard of errors in technics is much greater as far as the life of the patient is concerned in the older individual.

Intravenous injections

The cardiovascular apparatus of the older individual, as already discussed, is much less flexible than that of the younger individual. Moreover, the capillaries are probably much more permeable, and edema is more likely to occur. Increases in blood pressure are more prone to precipitate hemorrhage, and disparities between the systemic and the pulmonary circulation are more likely to lead to pulmonary edema. For these and other reasons, the use of intravenous injection must be carefully supervised in order to avoid excessive rates of flow which in general should not exceed 1 l. per hour in an average sized patient. In special cases, a manometer should be interpolated into the infusion set. This permits the surgeon to avoid excessive rates of infusion, for as long as the venous pressure remains under 100 mm. of water, there is little if any danger of overloading the circulation.

The amount of fluid infused must be much more carefully estimated in older patients lest superfluous fluid impose too great a diuretic task on the kidneys. As a general rule it is better for intravenous injections to err on the side of giving less than is needed than giving more. Moreover, the proper kind of fluid is much more important in the older individual because of the danger of imposing unnecessary excretory tasks upon the

kidneys. This applies to all fluid and food intake regardless of the route of administration, oral, subcutaneous, rectal or intravenous. For example, unneeded salt is readily excreted by the young kidney, but may lead to edema in older surgical patients because of the inability of their kidneys to excrete the excess. This also applies to blood and plasma transfusions, each of which should be used only for specific indications and the volume given based upon minimum needs. The benefits to be gained by intravenous fluids are just as great in older as in younger individuals, but at the same time, the dangers of giving the wrong kind or too much are greater than in the younger individual. Thus more specific and detailed knowledge is required in treating older patients so as to avoid the dangers which may come because the patient's renal and cardiovascular systems are unable to make up for our mistakes. Unfortunately, errors in therapy are still common but are less hazardous in younger surgical patients because they are able to compensate for them.

Early movement and ambulation

The advantages of early body movement and termination of bed rest have been extensively studied and are now definitely established in the therapy of most patients subjected to injury or operation involving bed rest. They are particularly applicable to the older age group. Long before early ambulation was used as a general postoperative procedure, practically every surgeon realized its importance after operation upon the older individual.

The use of early movement, sometimes called early ambulation or early termination of bed rest, is often misapplied. The early termination of bed rest after operation has merely a psychological effect upon the patient. Unless it is associated with definite walking, its use as a physical factor in surgical convalescence is apt to be lost. Indeed, there is some evidence that the patient who merely gets out of bed and sits in a chair with his feet resting on the floor suffers a decrease in blood flow from his feet and thus more vascular stasis than if he were kept in bed with his legs in the horizontal position. Moreover, there is also evidence that if bed rest is suddenly terminated (without previous exercise) at about the third or fourth day after operation, the danger of embolism may be increased, for it is at this period that the venous thrombus is long and most apt to be detached. If a thrombus is present in the lower leg veins, it is clear that without anticoagulant therapy, movement increases whereas rest in bed minimizes the likelihood of embolism. The same danger applies to a patient who has been kept immobile at rest in bed before operation and immediately after is forced to get up and walk. Moreover, movement as a preoperative as well as a postoperative procedure can be carried out with the

patient in bed as well as out of bed. The principles of therapy are more important than details, and these concern the need for increasing the rate of blood flow from the lower extremities. This should be started at the very beginning of surgical care, and indeed should begin before operation. It is the vascular stasis in the deep veins of the foot and lower leg which must be minimized or eliminated by early and continuous exercise of the lower extremities. This is the important factor in preventing thrombosis from which pulmonary embolism arises. Pulmonary embolism is an accident which is particularly prone to occur in the older individual after operation, and the most meticulous care must be taken to prevent its occurrence.

Another method of preventing thrombosis and of minimizing embolism is the use of anticoagulant therapy and this is superior to ligation of the femoral vein which in selected cases will prevent an existing thrombus from breaking off and producing an embolus.

Early movement is especially important in the aged following injury to bones and joints for reasons already discussed. Obviously, such therapy cannot be applied at the expense of losing the position of a reduced fractured bone. However, the need for muscular contraction is so great that even if the limb is completely immobilized, much will be gained if the patient is made to exert isometric contraction of the muscle frequently during his waking hours. Early movements of joints are also important and should be started as soon as possible.

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ANESTHESIA IN THE AGED

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There is at present a wealth of material for study in the field of geriatric anesthesia. This is due to at least two factors; first, to the increase in the actual number of persons over 60 years of age, and secondly, to the increased incidence of operative procedures which are now performed in this age group. In 1950, there were 17.2 million people over 60 years of age in the United States. With increased attention focussed on the early diagnosis of malignancy, many of these people are candidates for elective surgery, and of necessity, anesthesia. Furthermore, with improved surgical and anesthetic techniques, the operative morbidity and mortality has decreased to a point where the so-called "poor risk" patient is given the benefit of surgery (1). Turville and Dripps (2), in their series of 1,064 anesthetics to patients over 70 years of age, had a mortality of only 4.9 per cent. Dillon (3) reports a series of 707 anesthetics in the same age group, with a mortality of 8.17 per cent. In a study of 173 cases of patients with fractured neck of the femur at Bellevue Hospital (4), there was a 6.3 per cent operative fatality. Baird (5) has a series of 673 anesthetics in patients 70 years of age and over, with a mortality of 11.7 per cent. Although these statistics show an encouraging tendency from the former hazardous figures for geriatric anesthesia, the problem is still a serious one.

In dealing with the older patient, the anesthetist is confronted with the anatomical and physiological changes peculiar to senescence (6–10). These vary to a marked degree, and the chronological age may not be a true index of the individual's capabilities to withstand stress. The respiratory, circulatory and excretory systems are of primary interest. Throughout the respiratory tract, as elsewhere in the body, there is increased tissue fibrosis with loss of elastic tissue. The bronchi show atrophy of the mucosa. The bronchioles are narrowed, the alveoli dilated, with rupture of inter-

alveolar septa. The thoracic cage tends to become fixed. The pleura undergoes thinning and drying. With these anatomical changes, the physiology is disturbed. There is sluggish elimination of secretions from the respiratory tract. Emphysematous changes increase the tendency to hypostasis and atelectasis. There is increased abdominal and decreased thoracic respiration, decreased vital capacity and tidal exchange, and a compensatory tachypnea. There is a greater retention of carbon dioxide which may be due in part to a possible decreased permeability of the alveolar membrane. From an anesthetic standpoint, these changes point to a more complicated and prolonged induction, and a greater tendency to hypoxia. The recovery period will also be longer, with a greater incidence of atelectasis and hypostatic pneumonia postoperatively.

In the cardiovascular system, there occur arteriosclerotic changes in the blood vessels, with diminution of arterial elasticity and blood supply to vital organs. Of these, the most important are changes in the coronary vessels. Cardiac hypertrophy and myocardial degeneration appear. Hypertension may be an adjunct. There is an increased incidence of cardiac arrythmias. With the diminished plasma volume, and increased circulatory stasis, there is a greater tendency to thrombosis and embolism. Both sympathetic and parasympathetic stimulation may produce a decreased or abnormal response. Because of the anatomical and functional cardiac changes, cardiac decompensation is more frequent; the cardiac reserve is decreased. The cardiac decompensation may be subclinical, or accompanied by pulmonary edema, and chronic passive congestion of the liver and kidneys. One of the most important factors to the anesthesiologist is that the circulatory system has lost many of its compensatory mechanisms which in a younger individual allows him to withstand a stress situation, such as anesthesia may induce.

The liver and kidneys show the changes secondary to arteriosclerosis, and a proliferation of connective tissue, with a decrease in tissue cells. The resultant dysfunction affects the ability to detoxify and excrete anesthetic drugs.

There are other anatomical and physiological changes which must be considered, as contributing to the decreased reserve under stress which characterizes the elderly patient (1). Dietary requirements may be unfulfilled, because of poor appetite or bad dietary habits. There is a decrease in secretory activity and muscle tone. Because of incomplete absorption, the protein requirement is higher. Carbohydrate metabolism may be impaired. These factors affect the patient's nutrition, and therefore his resistance.

In estimating the anesthetic risk in any one patient, the degree of senes-

cent changes should be considered. Again it must be emphasized that age alone is not the standard. Some of the anatomical changes will be determined by physical examination. Others require laboratory tests, such as the electrocardiogram. All patients should have at least a urine examination, and a complete blood count. A chest x-ray should be routine. In so far as possible, efforts should be directed towards the maximum correction of existing abnormalities. This includes proper hydration and blood replacement; digitalization if cardiac failure is present or imminent; the oral administration of pronestyl for arrythmias where indicated; postural drainage and antibiotics in chest pathology; and correction of vitamin, mineral and protein deficiencies.

The anesthesiologist who sees the patient preoperatively plays an important role. Besides assessing the patient physically, determining the type of anesthesia most suitable, and ordering the premedication, he must win the patient's confidence. It is his job to allay the understandable anxiety, and reassure the patient as to the outcome of both anesthesia and operation. Many elderly patients are fearful, or at best resigned to their fate. Preoperative medication is given to all patients, whatever their age, for the same reasons (9). It is used to relieve apprehension, which is important not only as it affects the patient's comfort, but because of psychosomatic factors. Older patients are often more prone to psychic shock, because of early brain fatigue, and slow mental activity. Premedication is also intended to decrease secretions in the respiratory tract. Further, it lowers the metabolic rate, so that oxygen requirements are reduced, and the amount of anesthetic decreased. Premedication has another important application; to obtund reflex activity.

The choice of premedication is more difficult in the older patient (11). He absorbs drugs more slowly. Because of liver and kidney changes, he also excretes and detoxifies them over a longer period. Drugs which are eliminated through the respiratory tract are excreted at a slower rate. With a lowered metabolic rate, oxidation and conjugation are more prolonged. This means that doses must be smaller, and given at an earlier time preoperatively. Oversedation may be fatal in the elderly patient; it is preferable to err on the side of too little premedication. Although it is desirable for the patient to have a good night's sleep preoperatively, the use of heavy barbiturate sedation is not warranted. In general, barbiturates are not well tolerated by the elderly patient. They may produce respira- [illegible]

of an opiate. They are also useful as a prophylactic against procaine reac-

lists the following precautions for the use of spinal anesthesia in the elderly patient: (a) It is not used when the preoperative blood pressure is greater than 180 mm. systolic. (b) It is not used when there has been a drop of more than 20 mm. following premedication. (c) It is not used in anemia, disease of the central nervous system or recent shock. (d) The dose should always be kept small. (e) Ephedrine is given preoperatively. (f) The level of anesthesia is kept below the tenth thoracic segment. (g) Supportive therapy is given routinely, in the form of parental fluids or blood. He considers spinal anesthesia the method of choice in the lower extremities and pelvis.

Turville and Dripps (2), in their series of 1,064 patients over seventy years of age, used spinal anesthesia in 448. Of these, thirty-three per cent had a drop in blood pressure, but they state that most of these patients had no resultant cardiac damage. There were, however, nine cases of coronary occlusion; seven of those with a sharp drop in blood pressure. In Baird's (5) series of patients, he found that the largest percentage of complications involving the circulatory system followed spinal anesthesia. The other complication of high spinal anesthesia is respiratory depression, with its danger of anoxia during the operation, and an increased incidence of postoperative respiratory complications, including atelectasis and bronchopneumonia.

Several adaptations of spinal anesthesia are particularly useful in the older patient (14, 15). Saddle block is a form of intrathecal anesthesia which affects only the regions supplied by the lumbar nerves, or at the most the lowest thoracic segments, and therefore is attended by little or no change in blood pressure. The technique differs in that the patient is given a weighted solution of anesthetic agent, while in a sitting position which is maintained for a certain period of time. It is a good choice for rectal and perineal surgery. Continuous spinal anesthesia, with the intermittent administration of small amounts of agent, has the advantage that it can be used for lengthy operations, and the dose at any one time is minimal. Occasionally it is desirable to supplement the spinal anesthetic because of apprehension or nausea. This can be accomplished either by an inhalation agent such as nitrous oxide oxygen or cyclopropane, or by intravenous pentothal. The patient is kept in a light plane of anesthesia, with due regard for proper oxygenation.

The use of intravenous anesthesia in the geriatric patient should be attended with caution. Pentothal sodium is the agent of choice. Many of the contraindications to its use are often present in this age group, such as marked hypo- or hypertension, dyspnea, respiratory obstruction, and actual or potential cardiac decompensation. It is considered undesirable to use it in the presence of hepatic or renal pathology, although the exact

site of its destruction and elimination is not known. If given in dilute solutions, such as 0.2 per cent by intravenous drip, it is safe and useful for short operative procedures (16). When this is supplemented by a 50-50 mixture of nitrous oxide and oxygen, the amount of pentothal required is decreased, and adequate oxygenation is insured. This combination is used together with a muscle relaxant, for abdominal surgery, with good results. Intravenous anesthesia is also useful as an induction agent in apprehensive patients of any age. Respiratory and circulatory depression may occur with pentothal, and the postoperative narcosis is somewhat prolonged in older people. For these reasons, its use is limited.

Inhalation anesthesia comprises chiefly the use of nitrous oxide, ethyl ether, divinyl ether, ethylene and cyclopropane. These agents are combined in various ways, and given by numerous techniques, depending upon the experience and background of the anesthesiologist. Whatever the method and agent employed, the fundamental purpose is to obtain analgesia and muscular relaxation in the most physiologic manner possible. The most important single factor is the skillful management of the inhalation anesthesia (3, 9). Marked changes in blood pressure will result from asphyxia, either from obstruction or from inadequate oxygen in the inspired atmosphere. Accumulation of excessive amounts of carbon dioxide will also produce hypertension. A prolonged excitement stage during induction will increase blood adrenalin, and thereby elevate blood pressure. The accumulation of secretions in the respiratory tract, with resultant obstruction and laryngospasm, must be avoided

Nitrous oxide has a very limited application because it does not provide surgical anesthesia. It is a good analgesic and a good induction agent, provided that adequate oxygenation is maintained. Ethyl ether is an ideal muscle relaxant, but it has disadvantages in the older patient. It increases bronchial secretions, and produces a transient albuminuria. If liver damage is present, it should be used cautiously. There is also a rise in blood sugar, and a decrease in insulin production, so that it is not the best agent for diabetics. Induction is prolonged with ether, and care must be taken to avoid asphyxia and carbon dioxide retention. Recovery is also slower with this agent. Nevertheless, it still has the greatest margin of safety of any inhalation agent.

Divinyl ether, or vinethene, is useful for short procedures which do not require relaxation. It provides a rapid induction and quick recovery. Ethylene has been largely replaced by cyclopropane because of the latter's greater potency, but its uses are similar.

Cyclopropane is probably the nearest approach to the ideal inhalation agent because of its rapid induction and recovery, high potency, and the high oxygen concentration given with the gas (9). It is a parasympathomi-

metic drug, and does not increase adrenalin production. It is not irritating to the respiratory tract, and does not affect kidney function. There is no disturbance to the coronary blood flow with cyclopropane. The contraindications to the use of this drug have been the presence of arrythmias and the exhibition of digitalis at the time of operation. However, it is no longer felt that these are absolute restrictions to the use of this agent. Clinical experience has shown that it may be used safely in patients with auricular fibrillation and other organic heart conditions (17).

Arrythmias may occur under cyclopropane anesthesia, but they appear in patients without obvious heart disease as frequently as in cardiacs. The treatment for these irregularities is both prophylactic and therapeutic. Where arrythmias occur most frequently, or are most dangerous, as in intrathoracic surgery, or in cardiac patients, or during endotracheal intubation, the prophylactic administration of procaine intravenously tends to prevent ventricular arrythmias (18). Pronestyl hydrochloride, the amide of the ester procaine, is apparently more effective, less toxic and longer acting than procaine. The drug acts by depressing the irritability of the ventriclar muscle. When arrythmias occur under cyclopropane anesthesia, procaine or pronestyl is administered, or another agent, such as ether or ethylene, is added. The safety of cyclopropane anesthesia has been further increased by the use of muscle relaxants, which permit the anesthesia to be maintained in lighter planes.

In the geriatric patient, the balance of homeostatic mechanisms is particularly delicate, and for this reason, the work done by Hershey and Zweifach (19, 20) on the effect of various anesthetic agents on peripheral vascular homeostasis is of interest. The aged patient cannot compensate as well in stress situations, of which anesthesia and surgery are important examples. These authors found that regional procaine, cyclopropane, and morphine in therapeutic doses seemed to produce little, if any, impairment of the compensatory responses of anesthetized dogs subjected to hemorrhage, as evidenced by vasoconstriction of small arteries and arterioles, and active vasomotion. Pentothal showed an intermediate effect on these responses, and ether an unfavorable effect, as evidenced by vasodilatation and loss of vasomotion.

The muscle relaxants which have more recently been introduced into anesthesia, permit the great advantage of relaxation coupled with lighter anesthesia, not only with cyclopropane as was mentioned, but with other inhalation agents and also with sodium pentothal (21, 22). In the older patient particularly, it is desirable to use the minimum amount of anesthesia possible. The curare preparations, intocostrin and d-tubocurarine chloride, act by blocking the "nicotinic" action of acetyl choline and the nervous impulses to skeletal muscle at the myoneural junction. The dis-

advantage of these agents is the danger of respiratory embarrassment, and inadequate respiratory exchange. Since any anoxia is to be avoided in the older patient, the drug should be given in small divided doses, and the effect carefully noted. It may be necessary to supplement respiratory exchange.

Prostigmine methylsulfate is the pharmacological antidote to curare, but it is not successful except in moderate curare overdosage. Facilities for endotracheal intubation and artificial respiration should always be at hand. Curare is contraindicated where pulmonary deficiency is already present, or in kidney and liver disease. Decamethonium bromide (syncurine), which is a synthetic neuromuscular blocking agent, may prove to be of greater value in geriatric surgery (23). It has a more rapid onset and recovery of muscular paralysis, and it does not produce the histamine-like reactions of bronchospasm and hypotension which may occur with the curare preparations.

Cryotherapy, or refrigeration anesthesia, has a limited field of application in geriatric surgery. It has been used in operations on the extremities, such as amputations or embolectomies. If it is done properly, satisfactory anesthesia can be obtained, with good postoperative results. A tourniquet is applied, and there is little shock or blood loss The method is somewhat time consuming and cumbersome.

Supportive treatment during the operation is of great importance in the aged patient. Much of it should be prophylactic. Where blood loss or shock is anticipated, transfusions are the treatment of choice. Overhydration or the too rapid administration of fluids may result in pulmonary edema. The administration of analeptics for hypotension and shock is questionable in a patient whose compensatory mechanisms are already overtaxed. However, the use of drugs whose primary action is to increase cardiac output rather than peripheral vasoconstriction may be helpful. Since anoxia is to be avoided at any time, it is wise to give oxygen with spinal and pentothal anesthesias. The position of the patient is important, and marked changes in blood pressure and respiratory exchange may occur in the Trendelenberg, lithotomy and kidney positions. A careful tracheobronchial aspiration at the close of the operation will decrease the incidence of postoperative pulmonary complications.

The postoperative period is still within the scope of the anesthesiologist. The elderly patient is more prone to respiratory and circulatory complications, and again prophylaxis is the best treatment. He should be encouraged to turn frequently, to cough, and to breathe deeply. Early ambulation and prophylactic antibiotics aid in the prevention of pulmonary complications. Ambulation is also important in the lowered incidence of phlebothrombosis and embolism. Preoperative venous ligation, paraverte-

bral sympathetic blocks and postoperative heparinization are also recommended to prevent vascular complications. Fluid therapy must be carefully controlled, so as not to overload the circulation, and to provide adequate amounts of sodium, potassium, protein and vitamins. Sedation for pain relief should be as light as possible, so as not to produce respiratory depression, and not given routinely, but according to individual requirements. Many elderly patients may require no sedation. An intercostal block done with intracaine or nupercaine in oil will relieve much of the pain after abdominal surgery, and decrease the amount of sedation required. The intravenous administration of 0.1 per cent procaine in saline or dextrose produces analgesia, and by reducing tissue edema, may also promote wound healing. A solution of 5 per cent alcohol given intravenously, with dextrose or amigen, provides additional calories as well as satisfactory analgesia and sedation.

The problem of geriatric anesthesia resolves itself fundamentally to the choice of the least harmful agent and technique now available, which will fulfill the surgical requirements for the particular patient. The anesthesiologist is dealing with an individual in whom certain pathological processes are already under way, although he may be classified as a "good risk" patient. It is difficult to compare statistical data as to morbidity and mortality with various agents. The skill and experience of the anesthesiologist are intangible factors. Furthermore, there is a tendency to use certain drugs, such as pentothal, for minor procedures which do not entail the same risks as a laparotomy. Local or regional anesthesia is often reserved for the almost moribund patient, so that there is no equitable basis for comparison. Each patient must be carefully considered as an individual, and the surgeon, internist, and anesthesiologist must pool their resources to provide a successful outcome.

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33

DEGENERATION AND REGENERATION

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The importance of proper orientation in geriatric medicine needs to be emphasized. We must point out that the proper attitude should be the control and prevention of chronic disease, which must be done by evaluation of the bio-physical mechanism of the body of older people before disease strikes. It is of importance to evaluate this aspect of the body in all patients with manifestations of chronic disease (1). Those physicians who belong to the old school, or follow the pattern of conservative medicine—that of letting disease strike and then applying medicine—have but a small place in this field.

It is important to realize that the exhaustive processes which increase with age occur in all individuals past mid-life and that the sooner they are recognized and controlled, the better will be the health of the older population. Much has been said about physical rehabilitation, which is an important adjunct in chronic disease, but physical rehabilitation is, as a rule, of less permanent value in older people than in younger ones. This is due to the body changes in the oldster which make the recurrence of debilitation more likely. Since these factors are influenced primarily by geriatric medical care, the hand-in-hand approach of physical rehabilitation and proper medicine is of the greatest importance for the older age group.

In a discussion of body changes that occur with degeneration, which is associated with age and also of the ability of the organism to nullify these changes, it is necessary to analyze different features of the changes. In the first place, it is apropos to review the history of medicine in order to show that there has been a slow modification of the life span indicating that medicine and scientific knowledge may modify the course of events that

occur in nature as far as human health is concerned. The first American Life table, known as Wigglesworth's Table, was constructed for the year 1789 from data gathered from towns in New England. The span for the mean length of life at that time was found to be 35.5 years Progress in the modification of the life span following this period, statistics indicate, was slow and modification of longevity had advanced to only 40 years by the middle of the Nineteenth Century. By 1900 life expectation had jumped to about 50 years; by 1920 to 55 years, by 1930 to about 60 years, and by 1940 to somewhat over 64 years (2). The change was due to modification of the death rate under 40 years of age which was largely of a congenital, infectious or accidental origin, and the increased span of life resulted from bringing the causative conditions under control to a considerable extent.

Beginning at the age of 40, degenerative or exhaustive diseases which are associated with the ageing process assume a rapidly increased importance as the cause of illnesses. To emphasize the lack of medical control of these conditions, one may point out that an individual who had reached the age of 50 in 1900 had a life expectancy of 21 more years (3). An individual who had reached the age of 50 in 1940 still had a life expectancy of 71 years plus a few days. Such diseases as degenerative changes in the cardiovascular renal system, cancer, arthritis, diabetes, etc., lead the causes of death and disability. The disabled state that occurs in people suffering from these diseases is of extreme importance in geriatric medicine since many of the individuals become invalids and, as such, become wards of relatives, friends or society.

Ageing or Degenerative Changes

It is the opinion of the author that degenerative disease is not true ageing and that no one has ever lived long enough to die of true old age. Degenerative change always intercedes in one or many forms, to cause disturbance of body function, which in turn produces the diseases of age as we now know them.

It is of interest of break down ageing or degeneration as we see it in an infirmary. We may first evaluate degenerative disease by pointing out that there are, broadly speaking, usually two types of body changes seen, *exogenous* and *endogenous*. The former is a focal type of tissue change in which certain organs or systems may become diseased, and as a consequence decreased function of the body organism occurs. This change of tissue and tissue function is the result of an extraneous factor or factors, or disease, and for that reason is sometimes called *exogenous* ageing (fig. 1). It has also been considered to be the chronic phase of a more active disease process. This type of change is exemplified in an individual who has

developed pulmonary fibrosis due to silicosis. From the foreign body reaction of silicate in the lung, scar tissue occurs. Anoxia occurs due to thickened and scarred alveolar walls which results in a difficulty in oxygenation of the body tissue. The individual may become so short of breath that he is unable to eat and starvation with general changes in body stature ensues. Such a state leads to degeneration of the entire organism.

Exogenous factors which may cause degenerative body changes are not only exposure to substances which produce disease changes such as silicosis but certain infectious and occupational diseases, etc. Rheumatic fever



FIG. 1. Photograph of a 47 year old white man who appears clinically much older. The chronic disease which has affected him is pulmonary fibrosis as a result of silicosis He is an example of so-called exogenous body degeneration.

which attacks vulnerable areas of the body as well as specific and pyogenic infections may lead to a chronic disease as an aftermath of the acute process. Over-exposure to environmental conditions which are not compatible with health such as extreme heat or cold, or over-indulgence in tobacco, alcohol or food, particularly, as well as the lack of certain essential substances in the food intake take their toll and hasten degeneration. How permanent these changes are varies a great deal but it is my general impression that most deficiencies or over-indulgences carried on for a time will result in irreparable damage. It is well known that changes due to disease may persist and handicap an individual only moderately throughout early life, but may become much more severe in later life. Such a disease may be

an example of so-called exogenous ageing and the essential course is body degeneration, dependent upon a profound disturbance of a particular organ or system.

Physiological ageing which is the result of internal basic body changes is sometimes called *endogenous* degeneration. It is the type which we shall chiefly consider in this Chapter. We are all acquainted with those individuals who remain relatively healthy at an older age, say 80, and others who are in ill health at the relatively early age of 50. Anatomical studies at postmortem in these groups of individuals do frequently shed light upon the mechanism of body change (4). It is frequently found that those individuals who develop ill health as a result of endogenous degenerative diseases have generalized vascular changes. Such observations have led to the old adage that "one is as old as one's arteries." Anatomical study, however, does not reveal the physiological changes that have occurred in the individual which have led to the arterial disease. Postmortem findings do not necessarily assist one in the evaluation of the cause of the disease process. It is only through clinical and experimental study and evaluation of the many basic physiological principles that one may arrive at any conclusions as to principles involved in the production of such degenerative changes (fig. 2).

The endogenous factors which may cause degenerative changes are believed to be associated with inherited tendencies. It is considered that habit as well as environment may play an important role in the cause of degenerative body disease. The old saying "pick your ancestors to live a long and healthy life" may mean that certain individuals by inheritance obtain an organism that is more rugged and durable than the average but it also may mean that those ancestors may have been both mentally and physically alert to damaging conditions and hence did not indulge in factors which favor the occurrence of body degeneration. It is the author's belief that some degenerative body changes begin at quite an early age and may be, in part, related to the rate of oxygen consumption (5).

An example of exogenous ageing is seen in childhood where degenerative body changes occur which may be associated with growth of the body. This syndrome is known as progeria. Development of mental capacity and physical stature may continue to parallel the ageing process in these children. The mental capacity of the individual may exceed that of his brothers and sisters (6). Degeneration of the body is progressive in spite of the anabolic activity. By the time the child reaches the age of 10 to 13 he is a typical old man or woman. This change is believed to be due to disturbances in the endocrine glands (7) (fig. 3).

It seems likely that if the state of being of the body known as ageing

were simply one process, all tissues should decline equally provided their state remains constant. One might expect to find that the brain, the heart and all organs would have an equal span of life. In other words, one would expect that all tissues of the body would be like the wonderful "One Hoss Shay" which lived to a definite period and then broke up altogether. Anatomists tell us, and clinically we find, that one tissue and tissue function may do very well in older people, whereas certain other tissues may be the





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only ones varying from normal, indicating that disease has attacked certain tissues and not others. This in itself suggests that true ageing should be separated from the diseases that are now found associated with our so-called ageing.

Degenerative changes as a general rule begin in the tissues of the body that have been attacked by previous disease. Such tissues are those which have reduced their physiologic activity or are associated with congenital anatomical defects or inflammatory tissues with resultant scarring and deposits of calcium. Generally speaking, however, those tissues which manifest less than their normal activity are more prone to show degenerative changes than are those which continue their normal activity. Thus, the sex

organs as well as other tissues, may manifest degenerative changes at a relatively early age after cessation of function.

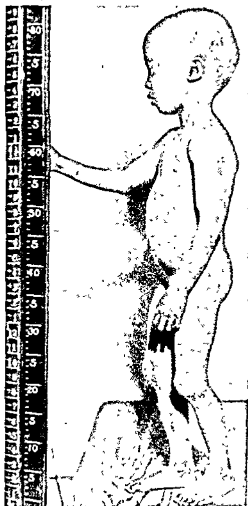


FIG 3 Photograph of a child with progeria, showing many of the typical signs of the condition, such as enlarged head, enlarged knees and prominent abdomen. This child died at the age of 10 of coronary thrombosis.

DEGENERATION

It is possible to ask the time-honored question, is degenerative disease inevitable in the process of ageing? If one were to answer the question in the affirmative, Warthin's contention that ageing is a wearing out process

would be supported (8). On the other hand, a more modern as well as a more optimistic view is that degeneration is a disease process which is only incidentally related to age. Perhaps we would obtain a better understanding of the question if we would discuss the relationship of the disease problem at the other end of the life cycle, that is, in youth, which had a high death rate prior to the advent of scientific medicine.

It is well known that lack of immunity in childhood sets the stage for the infectious diseases and greatly increases the incidence of debility and mortality. Now is it not possible that we may be dealing in this latter period of life with a similar set of circumstances in which cardiovascular renal disease, cancer and diabetes are the biological diseases of age analagous to scarlet fever and diphtheria in the unprotected child? If degenerative disease is a separate entity from age, yet dependent on a disturbed physiological principle associated with it, one may explain many of the clinical and biological points associated with these conditions. It would explain why some individuals live many years longer and also remain in better health than do others with the same family background.

I think it well at this point to discuss what is meant by degenerative disease. Degenerative changes have been described as those variations in form or function of tissue which bring the tissue substance to a decreased anatomical or functional state (9). It is known that this description may be applied to many disease processes. Anatomical and functional studies have shown that many tissues modify their functions under acute circumstances and may recover to a considerable extent (10). It is this, I believe, which explains the variation in activity of our bodies from day to day or week to week.

Degenerative changes must be considered in contrast to the acute as being the more permanent state of change and they have been divided into two forms (11), one, primary change or so-called true degeneration, a form in which there is a persistent decrease in functional activity and frequently a change in the architecture of the tissue. A second type is degenerative change which is a result of deposit of an abnormal substance in the tissues such as occurs in amyloid disease, etc.

An important question is, can the state of more prolonged decreased anatomical and functional activity be modified? Such modification should carry with it not only a change of the tissue to a more normal anatomical or functional state as found in younger individuals, but also definite evidence that disease is not produced by such a change. It is not within the realm of knowledge and experience at this time to give complete results in the study of modification of all tissue, but we can indicate changes in some. It seems to us that if we can re-establish normal body function in some degenerated tissue by application of sound medical principles without

producing disease, we can expect to modify the course of degenerative disease in other tissue.

The rate of oxygen consumption is of interest in evaluation of degenerative changes. The maximum rate of oxygen consumption is reached just before puberty (12) and we also find that the mortality rate for man is lowest at this period of life. What actually happens to the ever-changing rate of oxygen consumption beyond this period of life is not known. After the advent of puberty, there is believed to be a slow but variable decline in the rate of oxygen usage, that is, in different individuals there is usually considerable fluctuation from month to month and year to year. The greatest decline occurs after the age of 40, beginning with the period of menopause. From puberty to mid-life there is usually a cyclic change in the rate of oxygen consumption depending in part upon the body state. At the beginning of mid-life, with the progressive decline in the rate of oxygen consumption, degenerative changes begin to appear and tend to increase the rate of oxygen usage. It is believed by some students of the subject that the action of degenerative disease in modifying the rate of oxygen consumption is not directly related to the glands of internal secretion but is caused by imposing a strain on the functions of the body tissue. As an example, one may point to the influence of a pneumothorax on the basal metabolic rate. The rate of oxygen consumption rises in direct proportion to an amount of air injected into the thorax and declines at the same rate with removal of the injected air, even though obvious dyspnea may not be noted.

The principles for control of endogenous degenerative disease changes seem to lie in two directions, one, that of adequate and proper nutrition, and the other the application of physiological stimuli such as hormones and enzymes.

Recognition of the Degenerative State in the Human Body

Symptoms

Since early degenerative changes are not easy to recognize because of limited methods of testing, it is important that the physician learn to evaluate symptoms, and, in the early stages, they must be his primary guide. Likewise, in treatment the response of the patient may be a better guide to therapy than clinical tests. Symptoms as a clinical guide may be confusing since they are similar to symptoms in many other diseases. It is necessary that the physician studying symptoms be on the alert for disease processes other than those associated with degenerative changes. It must be realized that the primary symptoms depend on localization of the degenerative process; thus, the symptoms of arthritis and diabetes may not be the same. Generally speaking, a combination of complaints may be used

as a guidepost rather than any one single symptom. Often times, however, the attention of a patient may become so focused on one complaint that he fails to perceive others. It is impossible to cover the entire field in a single paragraph but some of the more common complaints may be mentioned. Weakness and tiredness toward the end of the day are commonly associated with degenerative change, as is muscle fatigue. Inability to keep up with routine physical or mental activities is a common complaint. Decrease in memory, especially for specific information such as names and dates, as well as a feeling of incapability may be noted. Many symptoms such as irregularity of the heart beat, moderate to mild dyspnea, tightness in the chest, etc., are common. Vasomotor reactions of various types may all be an indication of degenerative body changes when other factors have been ruled out. Complaints referable to the joints may be included in the list also. Pains in the chest, abdomen and other tissues must be carefully evaluated.

In a study of degenerative disease a physician should not be content to determine the state of only one particular tissue, but should study the tissue and the body's ability to function as well (13). Thus, it is necessary that we not only seek to determine the anatomical state of organs or systems of organs but also the functional state of these tissues as well. Besides the extremely important factors of observation and personal contact with the individual, it is well that we recognize these two criteria by appropriate tests as far as can be done.

It is my belief that the evaluation of degenerative changes from a functional standpoint is more important than evaluation of the anatomical state. A difficulty that exists is that there are few tests of a functional nature which have been adequately evaluated. It seems, however, of importance to list a few and to indicate some of the major ones that should be used by the geriatric physician. Tests of the circulation time may be valuable in estimation of the cardiovascular-pulmonary state. The electrocardiogram and x-rays of the heart and chest are important in the older person not only from the standpoint of function but also from the standpoint of the state of being. Modification of the latter as well as other tests may be used to estimate the cardiac output. The vital capacity of the lungs is of much value both for an estimate of lung disease and/or change in the thoracic cage.

Other tests of aid to the geriatrician are the determination of the basal metabolic rate if associated with the serum protein bound iodine level as well as the uptake of radioactive iodine. Since hypofunction of the thyroid gland has been linked with arterial degeneration these data are important (14). The body's ability to handle glucose as measured by the glucose loading test is important because of the probable degenerative influence of

disturbed carbohydrate metabolism. The nitrogen balance may be obtained by feeding a known amount of protein and measuring the nitrogen output. This measurement is of importance since many elderly individuals show a disturbed nitrogen metabolism. Tests for liver function may be considered but unless specific liver disease is found they are not wholly reliable. The blood cholesterol level may also be of value.

The sex hormone concentration in the body, both estrogen and androgen, has been linked with the production of degenerative body changes. With such consideration it is, in my opinion, important to maintain a fairly high estrogen content in the body of both elderly males and females. It is possible to estimate the estrogen content of the body by the glycogen content of the epithelial cells (15). The vaginal epithelium may be used in the female and that of the tongue or other tissue in the male. A simple smear of the epithelium may be made and stained with iodine (16). In the male the degree of androgenic activity may be noted from the study of the prostatic secretion (17). The excretion of the 17-ketosteroids in the urine (18) may give some idea of the adrenal gland function and, therefore, should be evaluated in individuals with degenerative disease. Some of the principles of the pituitary activity may be ascertained by noting the gonadotropic substance in the urine (19). Determination of the calcium and phosphorus ratio in the blood may be important since the latter may be increased when the function of the eosinophilic cells of the pituitary are increased. The concentration of the urine in the absence of kidney disease may suggest the degree of posterior pituitary function. Functional activity of the kidney (20) and of the gastrointestinal tract (21) as well as the bone marrow should receive consideration.

Regeneration

The changes occurring with age have been looked upon as non-reversible. Some studies carried on over the past six years at the St. Louis City Infirmary Hospital in the Division of Gerontology with the cooperation of the Department of Gynecology of Washington University School of Medicine are of extreme significance in answering the question of feasibility of modification of degenerative changes.

Elderly women from 65 to 85 years were caused to menstruate by the use of estrogens and progesterone (22, 23). Several groups of these individuals have been studied and at the present time, the longest period of study has been approximately six years. Several problems of gynecological interest were involved in this work but from a gerontological standpoint there were three important ones. One problem was the question of whether or not degenerative tissue can be revitalized to the point of restoring it to a functioning level. Elderly women were considered ideal subjects for this

study because of the knowledge of the sexual cycle in women and its modification by the so-called sex hormones. Another reason for choosing the elderly female was that any evidence of early disease changes could be recognized. All patients were carefully examined before the study and during it to recognize evidence of disease. A third reason for choosing the elderly female was that the uterus, after menopause, is small and fibrotic and the blood vessels leading to it become sclerotic. An opportunity is thus afforded to study the effect of increased physiological activity upon the organ and upon the blood vessels which lead to the organ. We were also interested in obtaining the physiological response of such tissue in an elderly body as we wanted to know if normal function such as menstruation could be established and, if so, could the process be maintained once a month for an indefinite period without producing harm to the body as a whole or to the uterus. Another problem that was of interest was that if the uterus was returned to such a state of function, what changes in the anatomical state of it and other tissues might one find? Would the uterus continue to function if proper stimulation were applied or might there be development of a disease process? The work of some observers such as Crossen (24), Korenchevsky (25), etc., has indicated that stimulation of the genital tract might produce disease. It was found in our studies that the tissues of the elderly individual could be revitalized and caused to function normally. We also found that when the tissue was so stimulated disease did not develop provided that physiological doses were used and attention was paid to the balance of the other endocrines of the body. The problem of geriatric interest in the study of regeneration by means of sex hormones was the influence these substances had on distal tissues. Studies were made by biopsy of the skin, of the skeletal muscles, and on the mucous membranes, particularly of the nose. An improvement has been found in functional ability of the skin as shown by elastic changes in this tissue (26). It has likewise been found that there is improvement, in some instances at least, in the glycogen content of the cells in these tissues. This change in glycogen has been noted also in striated muscle.

The anatomical changes in the mucous membrane of the nose are of particular interest. It has been found that in the senile indiviual the mucous membrane of the nose is thin and the cells flat with a change toward squamous epithelium. The subepithelial layer is thin and devoid of blood vessels (figs. 4 and 5). The glands and ducts are likewise small and the epithelium is no longer cuboidal but flat. In those individuals to whom estrogen and progesterone is administered for a period, changes in the mucous membranes of the nose occur. The cells lining the cavity appear more normal and consist of columnar epithelium. The lining cells of the epithelium may be noted to have redeveloped cilia which were totally absent in the early sections.

In the submucous glands the epithelium changes from a flat to a columnar type with an increase in size of the ducts as well as an increase in blood supply (27).



[illegible]

A comparison of blood vessels taken at autopsy from the uteri of the elderly individuals in a control group showed an advanced arteriosclerosis. Many of the large arteries were calcified and those in the uterine muscle revealed a marked hyalinization and degeneration of the wall. In contrast

the blood vessels of the uteri of individuals who had menstruated over a period of time were larger than the controls' even though deposits of cal-



FIG. 5. Photomicrograph showing the [illegible] same indi- [illegible] is shows [illegible] normal [illegible] younger people.

cium were seen in the media. The blood vessels showed also a significant loss of hyalinized material in the walls and a reappearance of normal tissue in place of the dense hyalinization always seen in the arteries of the control patients. Our interpretation of the anatomical study of these tissues was

that there is a lessening of the arteriosclerotic process which suggests that one of the causes of arteriosclerosis may be a reduction of the physiological activity of this organ. If these findings can be interpreted to apply to other tissues they would suggest that one of the causes of arteriosclerosis may be a general lessening of tissue function (28, 29).

These studies in older women indicate that degenerative changes associated with endogenous ageing may be reversible to the point that both the anatomy and functional activity of the tissue may be returned towards normal when adequate therapy is applied. It is not the intention of the author to build up a case for the use of sex hormones. Their administration must and should be done carefully and above all they should be used physiologically as over-dose or under-dose may lead to disease. It is the belief that when we know the principles of degenerative changes which occur in ageing, part of which is nutritional and hormonal, it is likely that revitalization of the degenerated tissue not necessarily of the sex organs alone, but doubtlessly of other tissue such as the heart, brain, etc., will occur as well. It is necessary to add that other techniques of stimulation will be sought and found. Our experience in the use of androgen, or the male sex hormone, in the role of metabolism will be discussed under nutrition.

Modification of Degenerative Changes

It is well in a discussion of this type for us to take up the specific principles that have been found for the modification of degeneration. Since degenerative processes are not well understood it is necessary that we discuss the principles that have been found that seem to tend to control or limit this condition. The more biochemistry evaluates the body processes, the more we appreciate that life is a multiplicity of chemical reactions; that food eaten must be broken down into its component parts and reassimilated. The former process is known as digestion The body through habit or through certain changes in function may be unable to digest the food substances and to break them into smaller component parts and to reassimilate them. In such instances the organism may then suffer for lack of adequate nutritional material. Thus, the failure to break down protein could be a cause of protein deficiency. It is well known that animals when not given adequate protein (30) may eventually develop a reduced amount of enzymes in the gastrointestinal tract.

In a preliminary study by us it has been found that some older people manifest inadequate enzymatic activity in the gastrointestinal tract. It is commonly known that hydrochloric acid may be deficient and very frequently the addition of this acid may aid digestion. It is extremely important for a physician in evaluating an older person to concern himself with possible gastrointestinal deficiencies and substitution therapy. It has

been our experience that hydrochloric acid and bile salts and some of the commercial enzymes when added to the diet may improve health in cases of functional disturbances in the older person. Those individuals who must be maintained on increased protein levels, and who have limited ability to digest the substance, are likewise benefited by supplementary administration of digestive enzymes. An approach may be the administration of amino acids, particularly in the form of hydrolyzed yeast. Such administration may be of value since amino acids favor the build-up of the body to digest increasing amounts of protein as well as the build-up of the body protein.

Another useful supplement to gastrointestinal digestion may be the use of vitamins and minerals (31). It is believed that in some cases increased amounts of phosphorous, calcium and potassium, as well as iron and the group of the so-called trace minerals are important. It is our belief that these substances particularly the vitamin group are best administered with the food. Thiamine, riboflavin, etc., may be administered and form an important part in metabolism. The trace minerals have received relatively little study in man but in some animals it has been shown that there is a very definite improvement of the general metabolism of the animal when these substances have been added (32).

Another extremely important factor in therapy is the addition of the products of the glands of internal secretion. It is essential for the physician to handle these substances carefully. The thyroid substance, which plays an important role in general body metabolism, has specific influences on protein, fat and carbohydrate utilization. It not only has an influence on the metabolic factors of the body but also is a direct stimulant of the sympathetic nervous system and of the vasomotor system as well (30). Thyroid substance is believed to bear a definite relationship to other glands of internal secretion, notably the pancreas, adrenal, pituitary and sex glands. In older people the use of thyroid must be administered with extreme care and certainly those individuals who have an over-active sympathetic nervous system should be given thyroid in small doses, but it should not necessarily be omitted even if the basal metabolic rate is not low. The blood iodine level or rate of iodine uptake of the thyroid gland is of value *in a consideration of thyroid administration. It has been our experience* that in attempting to modify the metabolic level with thyroid administration one should begin with a small dose and allow a slow increase of the substance only when it is necessary. Often times the use of an organic iodide before the use of thyroid may prove beneficial in older individuals.

The co-administration of many of the glands of internal secretion such as estrogens and androgens, adrenal gland hormones as well as the posterior pituitary gland factors may be of benefit. It is only with careful study of the blood iodine levels, the 17-ketosteroids and gonadotropic substances

that judicious administration of different hormones in older people may be utilized to establish a hormone balance in the oldster. Our knowledge of the ability of the glands of internal secretion to be stimulated is meager in individuals past mid-life We know there are progressive fibrotic changes in all gland tissue (34) as well as changes in some of the hormone concentrations in the blood (35). Knowledge of such variables may be one of the means of controlling the factors which lead to decreased body function and consequent degeneration.

A word of caution must be injected into a discussion of such work. Care must be exercised in stimulating the glands or in the replacement therapy lest one may unduly stimulate the body to increased function which might be harmful. Over-stimulation in the oldster of one group of organs may effect a hypoactivity in others. It is known that the thyroid and adrenal glands have an antagonistic yet at the same time a synergistic relationship. The medulla of the adrenal has more of a synergistic effect on the thyroid than does the adrenal cortex. This is shown by the inadequate response of the experimental animal to epinephrine after thyroidectomy, as well as by the sensitizing effect of adrenal cortex to the response to epinephrine (36). Such deficiency responses noted in the experimental animal may be seen in the old person and emphasize the need of both accuracy and caution in evaluation of the functional state of the body from an endocrine standpoint. Thyroid has a synergistic effect on the action of the sex glands, particularly on the estrogen group (37). The co-administration of such hormones may be indicated.

Degenerative disease referable to the circulatory system

The most important and the most common degenerative change is that seen in the cardiovascular system. Evaluation of the degenerative changes occurring in the cardiovascular system is important but not well understood at this time. Statements have been made (14) as to the criteria of vascular degeneration and do seem to fit fairly well the anatomical changes that are found in degenerative vascular disease. As age advances, particularly after 50 and somewhere about mid-life, gross anatomical and functional changes begin to be found in the circulatory system. Generally the first functional change referable to the system, of which people complain, may begin about 40 years of age. Vasomotor disturbances are most commonly seen in individuals during the menopausal period, which suggests that the early changes may be related to endocrine factors. "Hot flashes" are examples of such a phenomenon. Since degenerative changes in the heart, are usually related to disturbances in circulation, such as decrease in blood supply to the cardiac muscle, it is necessary for us to give in some detail the nature of the possible changes that occur in arterial de-

generation. There are at least two processes and perhaps more (38, 39) seen in degenerative arterial disease or arteriosclerosis, both of which, to my mind, are separate entities but which are frequently associated. One of the processes as revealed by anatomical changes, according to Lansing, Blumenthal and Gray (40), consists of a degenerative change first occurring in the elastic tissue of the blood vessel walls while the second process consists of a deposit of cholesterol substance in the intimal layer of the blood vessels. It can be demonstrated that hyperlipemia and cholesterolemia may be associated with atherosclerosis in the experimental animal and man (41, 42). This in turn is believed to lead to arteriosclerosis. According to Lansing and his associates (40) degeneration of the media is of greatest importance in arteriosclerosis. Such a change may begin at an early age but does not manifest itself to any great extent until later life. It has been our impression that the degeneration of the arterial wall may be related to the rate of oxygen consumption and nutrition.

Recent anatomical studies in man and in the experimental animal have suggested (42) that the thyroid gland may play a role in arterial degeneration. Experimental study of animals, both herbivorous and carnivorous, have indicated that the lack of thyroid activity may be a factor in arterial degeneration. Thus, the rabbit, which is herbivorous, when fed cholesterol in oil develops arterial degeneration. Administration of thyroid or organic iodine may increase the blood cholesterol level but does inhibit the deposit of the fatty substance in the arterial wall. It is of interest that male rabbits under circumstances of cholesterol feeding will develop atherosclerosis in a shorter period of time than the female, and the castration of the male will lengthen the period that it takes to develop atherosclerosis, whereas castration of the female will shorten the period of atherosclerotic development. The development of atherosclerosis in a chicken may be spontaneous, but in a dog high cholesterol feeding must be accompanied by inhibition of thyroid gland or thyroid removal. The exact nature of the influence of the endocrine factors as causative agents is not known. It is hoped that by a closer study of the arterial wall information may be obtained on the subject.

A study of a group of patients with low metabolism followed for a period of years to determine the relationship of vascular accidents and death during the period of observation has been made (42). It was found that the incidence of some manifestations of arteriosclerosis were much lower in individuals whose metabolism was maintained near normal by treatment with thyroid than in those who were not so treated. The administration of thyroid in those people who present low metabolism will result in a definite lessening of the incidence of vascular accidents such as coronary thrombosis and intracranial hemorrhage.

It has long been known that diabetes with the resulting insufficient carbo-

hydrate burning may be associated with arteriosclerosis (43). In my experience the control of the diabetic blood sugar level helps to prevent arterial disease. I have found that arterial degeneration may not only be favored in those individuals with diabetic glucose tolerance curves but with other types of abnormal glucose tolerance curves as well, particularly the flat curve. The individuals who seem to have greatest health in old age most frequently present a normal type of glucose tolerance curve. This applies to both intravenous and oral techniques of testing (44). Further discussion of this will take place under the nutritional section. It would seem, therefore, that an attempt to establish normal glucose tolerance curves is of importance in older people in prevention of degenerative vascular changes.

Arteriosclerosis does have a rather indirect effect on clinical symptoms; thus it may manifest itself by heart disease or by peripheral vascular disease, by mental disease, etc. The true nature of arteriosclerosis at this time is not definitely known. The finding of large particles of fat in the blood of individuals with arterial degeneration is of much interest but lacks confirmation. The work of Gofman (45) in which fractionation of the entire spectrum of lipids and lipid protein components in the serum has been done by ultracentrifugation may prove to be the answer. Degeneration of the arterial wall doubtless is a second factor.

Degenerative disease of the heart muscle may and does occur. This degeneration of the heart muscle may accompany the lack of such factors as vitamin B (44), thyroid function (47), etc. Early recognition of a deficiency and proper correction will re-establish a normal state of function of the heart muscle.

The condition which must be spoken of in connection with cardiovascular disease is so-called angina pectoris. This condition is commonly seen in elderly individuals and may be the result of reflex stimulation of the sympathetic system due to anoxia of the heart muscle, the result of degenerative vascular disease. In a number of instances, however, it appears not to be related to primary disease of the heart. The pain in such instances, although quite typical in distribution and severity, occurs in the chest. It has the earmarks of being associated with increased irritability of the sympathetic nervous system and may in some instances be controlled by factors which depress the sympathetic nervous system, such as iodides and the use of androgen as well as removal of foci of irritation such as the gallbladder.

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individuals with essential hypertension may be found to have some nutritional disturbance on the basis of endocrine activity (48). Such blood pressure changes have been found associated with conditions of the pituitary gland, particularly overactivity of the basophilic cells in the anterior pituitary, disturbance of the adrenal gland, insufficient function of the thyroid gland as well as over-activity of the gland. It is a common observation that individuals with uncontrolled diabetes who have hypertension may be greatly benefited by re-adjustment of the sugar burning mechanism. It is true, too, that hypertension may be an aftermath of an infectious process, particularly when involving the kidneys, and may be associated with pyelonephritis or chronic subacute glomerulus nephritis. One out of three individuals with hypertension have pyelonephritis (49).

Tumor growth

The question of malignant disease which is related to a degenerative state is of considerable interest because of the frequency of occurrence of this disease in older people. The relationship of cancer to degenerative changes is not understood. It is possible, in some instances at least, that the stimulation factor may be related to endocrine balances of the body. It has been found that testosterone therapy may inhibit growths and cause shrinkage of metastases in cancer of the breast (48). This is not permanent, however. Likewise, the estrogen groups have been found to be a relief in pain and halting the growth of cancer of the prostate in man (51). This again is not permanent and the best results are obtained by removal of the testicles.

Nervous and mental changes

Nervous and mental diseases in the older person cover a multitude of diagnoses and the field must be left to the neurologist for proper evaluation. It is enough to say that senile psychosis and mental degenerative states, commonly thought of as arteriosclerotic in origin, may be modified to some extent by a high protein and adequate vitamin diet and by the use of hormone substance as indicated. A great deal of work must be done in establishment of the role of these particular factors. It has been shown that the feeding of low protein diets (52) frequently makes elderly individuals nervous, irritable and psychotic, whereas increased and adequate amounts of protein may improve the mental state in older people. The influence of sex hormones on the personalities and mental function of older people has been studied by Caldwell and associates (53). They have found that intellectual activity, although not uniformly at a high level in all its manifestations, does show some improvement in so far as ability to think and willingness to expend intellectual energy are concerned. Memory appears

definitely enhanced, particularly in respect to meaningful, logical material. Even in areas where there is no distinct intellectual improvement, there is often less of the decline than would have been expected by virtue of the increase in age of the subjects between the two examinations. Furthermore, the patients demonstrate to some degree a decrease in rigidity of thought processes and habit patterns and an increase in general motivation to succeed and cooperate.

Nutrition in general

Nutritional problems in the individual past mid-life are of extreme importance. The first problem begins about mid-life and is usually associated with a gain in weight. This gain in weight in some few individuals is believed to be due to disturbance of the endocrine mechanism but a great part of the change is due to over-indulgence in food and decrease in activity. The individual at the period of life between 45 and 65 usually retains a very good appetite. The gain in weight is often associated with a tendency of the serum protein-bound iodine level to drop as well as a drop in the basal metabolism and decline of activity of the sex glands. It is during this period of low metabolism and over-indulgence in food from the standpoint of the patient's needs that degenerative change becomes obvious. Throughout this period a limitation of sugars, and fats in the diet is important.

In order to maintain adequate nutrition, the patient should be on a diet of vegetables, fruits and lean meat with only moderate fats The food intake should closely balance with the rate of oxygen consumption. It is of interest, too, that during the period (45–65) there begins a more constant deviation from the normal glucose tolerance curve in an increasing number of individuals. It has been found by us that glucose tolerance curves more frequently vary after the age of 50 than they do at any time previous. Between the ages of 50 and 80 about 93 to 95 per cent of individuals show a very persistent abnormal glucose loading curve when the substance is given either by mouth or intravenously. In a study in our hospital of a group of people given a diet of 30 per cent of fat the mortality rate doubled in two years.

Recent work has indicated that the ability to utilize protein decreases in people past mid-life. It has been found that older people tend to develop a state of negative nitrogen balance more readily than do younger ones, and once they have developed such a state it is more difficult to readjust them by feeding protein.

In our experience, the use of androgen, particularly testosterone, has a decidedly influential role in improvement of utilization of protein in older individuals. It seems that in the older person when muscles become flabby and show signs of general decline the use of androgen is indicated.

The use of vitamins has been considered important according to the work of Chieffi and Kirk (54). It has been found that vitamin A blood levels may be decreased in some older individuals but generally speaking such is not the case.

Thiamin blood levels in 10 per cent of the older individuals examined were found to be lower than 2.0 µg. per cent (55). There were many symptoms presented by the individuals, such as general fatigue, redness and fissures of the tongue, abnormal gums, pigmentation of the ischial tuberosities, conjunctiva thickening, impaired vibration sense in both upper and lower extremities, impaired lower abdominal reflexes, edema and fluorescence of the tongue. Thiamin deficiency may be characterized by a smooth, reddened tongue in mild cases and severe encephalopathic symptoms in which the patient is stuporous, disoriented and may have hallucinations. Cogwhell rigidities and sucking reflexes present a picture similar to toxic psychosis or exhaustion delirium.

Ascorbic acid deficiency is characterized by swollen, spongy gums, increased capillary fragility and tendency to hemorrhage into the skin. Such changes have not been frequently found in our study.

Riboflavin deficiency as described in the aged is characterized by a colored tongue, fissures in the angles of the mouth, reddened lips, etc.

Vitamin D deficiency probably can occur but no details have been worked out.

Vitamin K deficiency may occur in liver or gallbladder disease in the event of a disturbance of the flow of bile to the intestinal tract.

Deficiencies of both calcium and phosphorus may occur in older people, particularly calcium. Likewise, under certain circumstances iron deficiency may be present.

Influence of glands of internal secretion on general metabolism

The pituitary gland is one of the more important glands of internal secretion in the body since it regulates other glands of internal secretion. In addition, it does have important functions within its own right such as control of the permeability factor of the cells of the kidney, water and salt metabolism, as well as an influence on carbohydrate, protein and fat metabolism. It is found that, generally speaking, in older people there may be a decrease in size and function of this gland.

There are many factors which may cause degeneration of the pituitary gland, such as infection, decreased blood supply, etc. Typical degenerative changes have been found in Simmond's disease. Replacement therapy under conditions of prolonged deficiencies of the pituitary gland is of importance in the armementarium of the geriatric physician. In the treatment of water and salt disturbances administration of posterior pituitary is beneficial.

The use of the powdered posterior lobe through a nasal insufflator or by injection of pitressin may correct these deficiencies. In some older people, disturbance of urinary function may be relieved by insufflation of the powder.

The thyroid gland has been discussed in its usage and possible relation to arteriosclerosis, particularly the state of hypothyroidism. As life advances there is frequently an atrophy of the thyroid with a reduction of the total amount of iodine content. Such a state varies in different individuals. Its action on the metabolism of carbohydrate, protein and fat is involved in the process of ageing. The replacement therapy of this in older people has to be managed with caution. Only small doses, $\frac{1}{10}$ to $\frac{1}{4}$ gr, should be given at first and the dosage slowly increased if indicated.

Very little is known about possible alterations of the parathyroids in older people. Doubtlessly they do undergo some tissue change which probably have some effect on the skeletal system.

The adrenal glands in the process of ageing show a decrease in size. There is probably an atrophy and a decrease in function of the cells of the glands. The 17-ketosteroids which may be used to determine the degree of function are found to be below normal or somewhat decreased in amounts compared to normal younger individuals. The work of Fraser (19) indicates that the ketosteroids are definitely diminished in men past 70. The findings suggest that many of the conspicuous symptoms of old age, such as loss of muscular energy and exhaustion, are suggestive of inadequate function of the adrenal cortex and, as a consequence, the muscular metabolism is on a lower plane. Not enough attention has been paid to this important study.

Perhaps better understanding of the function of the adrenal cortical substances will come when more experience is obtained with ACTH and Cortisone. Cortisone, we know, is involved in the metabolism of the carbohydrate, protein and fat. It inhibits neuro-muscular metabolism, and has distinct immunological effects.

Some have thought that the fibrous state of the adrenal may be responsible for the progeria syndrome. This, however, has never been fully established.

Pancreatic insufficiency, particularly from the standpoint of the glands of internal secretion, is characterized by that condition known as diabetes mellitus. This represents one of the most common instances of endocrine disturbances.

In 1938, 35 out of every 1000 individuals were found to have diabetes. This condition is not definitely a disease of senility but the incidence increases as individuals grow older. In our experience at the St. Louis Infirmary, the greatest incidence was in the age group between 60 and 70

and the percentage of individuals affected may run as high as 22 per cent in some groups. The curve of incidence indicates that it rises to its highest peak at the sixth decade, after which there is a gradual fall. The incidence after the age of 25 is higher in women than in men, being 1 out of every 45 women at the age of 65, and 1 out of every 70 men at the same age. The changing incidence of diabetic mortality is most apparent in the older decades of life, so much so that the increased diabetic mortality includes many individuals in the older age group. Since the introduction of insulin, deaths from diabetes of individuals under 50 years of age have shown a marked decline. The increased incidence of this condition in older people is due to three factors: one, the ageing of the population in general; two, the increased duration of life for the modern diabetic due to the use of insulin and better dietary understanding; and, three, the greater attention to better diagnosis of the disease in the ageing person. It has been found by us, in an infirmary hospital where initially the diabetic was not treated, that the mortality rate was quite high and the average age at death was 57 years. After the introduction of modern methods in the control of diabetes in the older individuals, the mortality rate changed and approached that of 72 years in those individuals treated.

It is extremely important in the study of elderly people to perform glucose loading tests for many reasons but particularly for the purpose of recognizing the diabetic. The blood sugar may be extremely high before sugar is found in the urine. Such a condition does not necessarily exist in young people.

Skeletal changes

Certain changes in the bones may be said to be a common occurrence in ageing although they are not limited to or always associated with degenerative changes. Idiopathic osteoporosis, particularly, is a factor that is associated with it. This condition may be associated with thyroid dysfunction or may be seen in individuals with simple primary bone changes. Likewise, functional disease of the parathyroids has been reported associated with it. Hypophyseal dysfunction may be seen in osteoporosis, particularly in elderly women and it is sometimes accompanied by hypertension and obesity. Such a condition may be seen in Simmond's disease, which is characterized by a change attributed to the anterior pituitary (56).

The recognition of underlying disturbed endocrine factors (57) with proper correction and the administration of calcium with vitamins A, D and E may halt the degenerative process.

Osteomalacia, which is characterized under x-ray by a washed-out appearance of the bone and scant trabeculations, is a factor in the kyphoscle-

rotic individuals. This condition is frequently associated with improper nutrition. The sodium-calcium may be low as is also the fat-soluble vitamin D

Physical activity after mid-life

It is my opinion that too much cannot be said for physical activity in the older individual. About the age of 40 the general trend is for the individual to become more sedentary, to decrease physical activity and, at the same time, to decline in mental reactions. Physical activity, although not to the extent of former years, should be encouraged in older people. The recent work of Rusk (58) has demonstrated that in chronic disease rehabilitation must be done with both mental and physical training. In substantiation of this one may point to the fact that a rural population tends to stay healthier to a later age than does a urban one. The psychological aspect of activity maintained is an approach which affords considerable opportunity for development.

Summary

A brief clinical review of present knowledge of degenerative body changes and their modification point up the inadequacy of study of chronic diseases associated with ageing. That more and more emphasis must be placed on the fundamental biochemical and physiological problems of ageing and exhaustion is apparent. This should be accomplished by emphasis on the functional as well as anatomical aspects of chronic disease. It is my belief that when we find methods for study of functional changes in the body the problem of degenerative disease will be understood and controlled and that the span of health will be greatly extended.

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COSMETOLOGICAL ASPECTS OF AGEING

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This chapter is devoted to a brief description of the changes in the skin and facial contour that occur with age and which result in a loss of esthetic appeal. Although the changes to be considered do not necessarily result in disease or even in limitation of body function they should not be dismissed as unimportant. It must be admitted that the deterioration in appearance and the frequent gross disfigurement which accompany bodily ageing contribute to no small degree to the dread with which later life is approached and serve to render distasteful this period of life even to those who escape crippling disease. For those whose ability to earn a livelihood depends on the maintenance of a youthful or attractive appearance, these changes are feared almost as much as organic disease. In almost all individuals the disfigurements of age make even more difficult the adjustment to this period of life.

Age produces alterations in the appearance of the skin of the entire body but we will limit our more detailed descriptions to the face and neck since these areas are the most important from the cosmetological point of view.

The changes which occur with age in these regions will be divided under three headings:

1. Production and accentuation of the lines of the face and neck.
2. Changes in the structure of the skin with age and the formation of wrinkles.
3. Changes in the facial contour with age.

Lines on the Face and Neck

Certain groups of muscles by their contraction cause repeated creasing of the skin and eventually produce permanent lines in the skin. The muscles

which produce the lines on the neck are the skeletal muscles responsible for the movements of flexion, extension and rotation of the head and neck. The lines on the face are the result of repeated contraction of the intrinsic facial muscles. The mechanism involved is not identical for the two groups of muscles. The shortening of the skeletal muscles during contraction causes the overlying tissues to become redundant and produces folding of the skin and also of the subcutaneous fatty tissue. The intrinsic muscles of the face are inserted for the greater part into the dermis and by their contraction not only cause the overlying skin to become redundant but actually exert a direct pull on the skin causing it to be folded upon itself without cushioning effect from the subcutaneous fatty tissue. The lines on the neck are usually broader and less sharply defined than those of the face except in more advanced age when the loss of subcutaneous fat results in deeply incised lines even on the neck. The presence of lines on the neck is not of itself a manifestation of age since certain creases are found on the neck even in childhood. Although the position of these creases is not absolutely constant there is a certain uniformity in their distribution. In youthful persons these lines are parallel horizontal curves, confined to the anterior aspect of the neck. Lines are usually found at the junction of the neck with the chin, at the level of the upper border of the thyroid cartilage, at the level of the lower border of the thyroid cartilage and at the base of the neck. Frequently instead of a single line in these situations there are two parallel creases. With advancing age these lines become prolonged laterally and upwards and numerous new lines appear at the side of the neck parallel with the angle of the jaw. These lateral lines begin to appear in the third decade and by the fourth decade are usually clearly marked. At the same time as these lateral lines appear, a line is formed on the face which is due to flexion of the head and is not produced by the intrinsic facial muscles. This line passes under the chin just posterior to the base of the mandible and extends up on to the cheeks for a variable distance.

In the fourth and fifth decades lines begin to appear on the back of the neck. There is usually one transverse line at the level of the hair line but the number and distribution of the other lines is very variable. There may be only one or two oblique lines or as many as eight or ten crossing each other and dividing the skin into numerous diamond shaped areas (fig. 1). These lines are much more pronounced in men than in women and are especially so in those who have been exposed to the weather. Pinkus (1) has given a detailed description of the varying patterns produced by these lines. In the condition known as elastosis senilis these lines are very conspicuous in the thickened skin and produce the characteristic appearance of "turtle neck".

The skin of the face differs from that of the neck in that it is normally unlined in youth. The first lines usually begin to appear toward the end of the second decade and become more numerous and prominent with the passing years (fig. 2).

The first lines to appear are usually the horizontal lines on the forehead which are occasionally discernible as early as the fifteenth year. These lines are produced by the frontal portion of the occipito-frontalis muscle. The typical lines produced by this muscle are concave upwards in the middle of the forehead and convex upwards at the outer extremities.

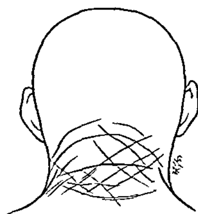


Fig. 1

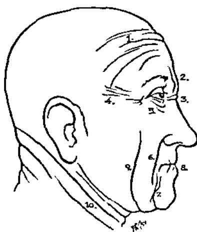


Fig. 2

Fig. 1. Transverse and oblique furrows at the back of the neck

the head

They vary in number from three to eight. The two bellies of the frontal muscle take origin from the epicranial aponeurosis at the level of the coronary suture and pass downwards towards the supra-orbital arch to be inserted into the skin and subcutaneous tissue over the eyebrows. The two parts of the muscle converge distally and are separated above by a triangular aponeurosis. The dip in the lines in the middle of the forehead corresponds to this aponeurotic area.

The vertical lines at the root of the nose are produced by the action of the corrugator supercilii muscles which take origin from the supra-orbital margin deep to the frontalis muscle and are inserted into the skin of the medial half of the eyebrows. Contraction of the muscle pulls the eyebrow downward and forward making an angle in the brow near its inner end.

In many persons contraction of this muscle is unconscious and almost constant and results in deep vertical lines at the root of the nose even at an early age. In contrast to these vertical lines, the transverse wrinkling at the root of the nose is produced by the procerus muscles which take origin from the fascia covering the lower part of the nasal bone and are inserted into the skin over the glabella.

Another line which frequently appears towards the end of the second decade is the nasolabial line. This line is frequently quite deep and conspicuous even in relatively young individuals. The line is formed in the nasolabial sulcus which is a depression of the facial tissues found in all faces even in infancy. The sulcus extends downwards and outwards from the wing of the nose to a point lateral to the angle of the mouth.

There are two reasons for the precocious and frequently exaggerated development of the nasolabial line. One is the fact that several of the muscles of facial expression have a partial insertion directly into the skin of the nasolabial sulcus. The other is the fact that many of the muscles of expression are inserted into or blend with the fibers of the orbicularis oris. This muscle, except for the small superior and inferior incisive bundles, has no bony attachments and confers great motility on the lower third of the face. This motility results in marked creasing of the skin in all changes of facial expression. The muscles which are inserted into the nasolabial sulcus are the levator labii superioris alaeque nasi, the levator labii superioris and the zygomaticus minor, which are all partially inserted into the skin of the nasolabial sulcus and into the upper lip. The muscles which contribute to the formation of the nasolabial line by elevating the upper lip and thereby deepening the nasolabial sulcus are the zygomaticus major, which takes origin from the zygomatic portion of the zygomatic arch and is inserted into the orbicularis oris muscle and the skin at the angle of the mouth; the levator anguli oris or caninus, which arises from the maxilla below the infra orbital foramen and is directed downwards to be inserted into the orbicularis oris and the skin at the angle of the mouth, and the risorius muscle, which is in part a continuation of the platysma of the face and in part an independent muscle which takes origin from the parotid fascia and passes transversely to be inserted into the skin at the angle of the mouth.

In the fourth decade another line appears in the region of the mouth. This line usually extends from the angle of the mouth outward and downwards but it may be directly continuous with the nasolabial line. The muscles which produce this line are the depressors of the lower lip, the depressor anguli oris or triangularis and the depressor labii inferioris; both of which pass upwards from the mandible to be inserted into the orbicularis oris and the skin of the lower lip.

Lines around the eyes do not usually appear until the fourth decade and their appearance is a sure sign of ageing of the skin.

The radiating lines at the external angle of the eye are produced by the orbital portion of the orbicularis oculi muscle. This section of the muscle has thick fibers which are attached to the supra-orbital notch and the infra-orbital foramen. At the outer angle of the orbit, however, the fibers have no bony attachment but are inserted directly into the skin.

During forcible closure of the eyes these lateral fibers produce the radiating creases or "crow's feet" at the angle of the eye. The lines in the lower lid which appear about the same time as the crow's feet are produced by the zygomaticus major muscle which pushes up the muscle mass of the cheek during laughter and results in transverse wrinkling of the lower eyelid.

In the fifth decade radiating lines frequently appear around the mouth. These lines are produced by slight general contraction of the fibers of the orbicularis oris muscles, resulting in constant compression of the lips and puckering of the skin.

Excellent descriptions of the facial muscles and their actions have been given by Roberts (2) and Philipsen (3).

Histological studies of the wrinkled areas of the skin have shown that the lines, except in the very young, are not mere infoldings of the epidermis but are associated with definite structural changes. Volarelli (4) in a study of skin obtained at autopsy found marked differences between the structure of the skin in the depth of the wrinkle and the surrounding unlined skin. At the site of the crease, the epidermis thinned abruptly, there being only 2 or 3 layers of epidermal cells with no evidence of a stratum granulosum.

The papillary processes were entirely lacking; the junction of epidermis and cutis being represented by a straight line. In the dermis the changes were most evident in the deeper layers where the connective tissue fibers were found to be poorly staining and to have elongated nuclei. The typical net-like arrangement of the fibers was lost.

In old individuals the collagen had undergone basophilic degeneration. Himmel (5) reported very similar findings but noted changes in the collagen fibers in both the superficial and deep layers of the dermis. Artz (6) in addition to the changes reported by these authors noted alterations in the elastic fibers. The elastic fibers in the wrinkles were much thinner than in the surrounding skin. They were broken, had lost their typical wavy outline and stained with basophilic dyes.

The creases in the skin of young persons were mere undulations of the surface with no structural change, but the alterations described were evident in early adult life. Even in elderly persons with markedly atrophic

skin, the atrophy was always more pronounced in the wrinkled areas than in the surrounding skin.

Changes in Skin Structure

The characteristic appearance of aged skin is due not only to the presence of the lines described above but also to certain changes in the quality or texture of the skin. When the skin of youthful persons is examined closely it is seen to be divided into innumerable rhomboidal areas by the criss-crossing of very fine lines. The lines or depressions correspond to downward projections of the epidermis, and the ridges to papillary projections of the dermis. When the skin is relaxed as for example over the dorsal aspect of the hyperextended wrist, the rhomboids have a much smaller surface area than they have when the skin is stretched by flexion of the wrist. This ability of the skin to take up slack and remain closely adherent to the underlying structures is due in part to the tone conferred on it by the action of the arrectores pilorum muscles. These are minute multiple fasciculi which are found in connection with the hair follicles and which pass from the papillary portion of the corium to be inserted at several points into the outer layer of several adjacent hair follicles. Contractions of these muscles result in an approximation of the epidermal lines and a narrowing of the rhomboidal areas.

The degree of elasticity conferred on the skin by this arrangement has been shown by Pinkus (1), who was able to demonstrate that the distensibility of the skin is much greater when a force is applied across the lines than when it is applied in the direction of the lines. He excised portions of skin from the anterior aspect of the thorax and stretched them by applying a 10 g. weight. He found that when a piece of skin 25 mm. long was stretched in the direction of the long axis of the ridges, it could be extended to a length of 29.5 mm., whereas when the stretching force was applied at right angles to the long axis of the ridges it could be extended to a length of 35 mm.

The distensibility of the corium is due to the presence of collagen fibers although collagen itself is not elastic. The bundles in the corium have a nest-like arrangement which allows for considerable distension. The elastic fibers in the corium serve to prevent overstretching of the collagen network.

The fine rhomboidal markings of the epidermis impart to the skin surface a rather dull sheen. As a result of ageing the number of papillary ridges is greatly reduced and the skin surface loses its mat appearance and becomes very smooth and glossy. When the skin becomes redundant during movements of the body the slack is no longer taken up by the mechanisms referred to above and crinkling of the surface results. This wrinkling of the relaxed skin is usually apparent by the sixth decade. In the later decades

loss of subcutaneous fat results in permanent redundancy of the skin which hangs loosely in coarse folds. Figure 3 is a photograph of the skin of an 80 year old female and shows clearly the glossy atrophic skin gathered into crepelike wrinkles (fig. 3).



FIG. 3. Atrophic wrinkled skin of forearm of 80 year old woman

Histological studies of the skin at this stage show marked alterations in structure. Goldzieher (7) in investigations on senile skin demonstrated atrophic changes in all layers of the skin. He found reductions in the number of cell layers in the epidermis and also in the number of epidermal pegs. In the cutis there was hyalination of the collagen fibers with wide-

spread fragmentation and a definite reduction in the number of nuclei. The elastic fibers had also become fragmented and showed basophilic degeneration.

That the aged skin has lost, to a great extent, its contractibility has been demonstrated by Evans, Cowdry and Nielsen (8). Studies by these authors showed that skin excised from the antecubital fossae of young adults shrank 46 per cent, whereas the shrinkage of skin from corresponding areas of old persons averaged only 12 per cent. Bönniger (9) observed the shrinkage of skin obtained at necropsy and found that the mean shrinkage in 11 young adults was 41 per cent, and 25 per cent in 6 old individuals. A dimunition in the elastic properties of intact skin has been demonstrated by Kirk and Kvorning (10). Using a modification of an apparatus designed by Schade in 1912, these investigators were able to measure the indentation of the skin produced by the application of a 50 g. weight and the skin rebound following removal of the weight. In a group of 24 young individuals they found that the immediate rebound of the skin following removal of the weight averaged 76 per cent of the total indentation, while in 28 old individuals the immediate rebound was only 43 per cent.

Changes in Facial Contour with Age

The alterations in the appearance of the face and neck which occur with age are due only in part to the lines and wrinkles described above. An even greater loss of esthetic appeal results from ptosis of the tissues and the formation of characteristic folds and pouches. That this is the case is obvious if one studies retouched photographs of older persons. In such photographs the lines and wrinkles have been eliminated but the age of the subject is betrayed, nevertheless, by the facial lineaments. There are several factors responsible for this ptosis of the facial tissues. One of these is the loss of elasticity of the skin, which has already been described in detail above. That atrophic changes in the skin can result in marked ptosis of the integument is illustrated by the disease known as chalazodermia. In this interesting condition, of which cases have been described by Von Kétly (11) and Carney and Nomland (12) there is marked atrophy of the skin of young individuals. The histological changes correspond almost exactly to those described in senile persons. Although the subcutaneous tissues are not affected, the marked inelasticity of the dermis itself results in the folds and pouches of the skin which are the outstanding features of the condition.

With advancing age, not only does the skin become inelastic but progressive atrophy of the subcutaneous tissues results in increasing redundancy of the integument. There is loss of subcutaneous fat and the buccal fatty pad is diminished in size. The importance of the facial muscles in main-

taining facial contour has been stressed by several authors. MacMillan (13) and Brown (14) consider the muscles of mastication of especial importance in this regard and attribute the drooping of the cheeks in great part to loss of muscle volume. Along with the atrophy of the muscles there is frequently a concomitant fibrosis which results in shortening of the fibers and an accentuation of the lines produced by the muscles. Finally, in more advanced old age, there is atrophy of the bones of the face. Goldstein (15) showed that there is diminution in almost all the facial measurements with advancing years. The only facial measurement which is not diminished with age is the length of the nose, which actually increases throughout life. The most pronounced changes are found in the maxilla and mandible and there is a marked decrease in the intermaxillary dimension. Loss of teeth and the resulting absorption of the alveolar processes are the factors responsible for this shortening of the lower third of the face. In addition there is a widening of the angle between the body and the ramus of the mandible. Hellman (16) has shown that most of the changes in the jaws which are associated with senility are the result of loss of teeth and are much less marked in persons who have retained their teeth than in edentulous individuals of the same age. As a result of these changes in the structure of the face, considerable redundancy and sagging of the overlying skin is produced.

The deformities produced by this ptosis tend to be very constant and have been well described by various authors, particularly Passot (17) and Claoué (18) (fig. 4). The areas most frequently involved are the following:

As a result of ptosis of the frontal region, the horizontal and vertical lines are converted into folds and the forehead remains permanently furrowed.

Ptosis of the temporal skin causes a descent of the outer angle of the eye and drooping of the upper eyelid.

Sagging of the skin of the lower eyelid results in the formation of pouches, which are made even more conspicuous by herniation of fatty tissue from the orbit.

The contour of the lower third of the face is the most markedly altered with age. Loss of the buccal pad of fat, atrophy of the masseter muscle and diminution in intermaxillary dimension combine to produce loss of volume of the part of the face and result in considerable ptosis of the cheeks. The nasolabial line is converted into a loose fold which is prolonged down toward the inferior border of the mandible. Folds are formed posteriorly, passing from the anterior aspect of the ear to the angle of the jaw.

In the region of the border of the mandible the skin is no longer adherent but hangs loosely to form jowls laterally and double chin in the mental

region. The formation of double chin instead of a single submental pouch is due to the muscle transversus mentis of Santorini, which forms a sling under the chin. The muscle is formed of fibers from both triangularis muscles.

In the region of the neck the redundancy of the skin tends to become very marked. There is considerable loss of vertical dimension of the neck due to narrowing of the intervertebral discs and absorption of the bodies of the vertebra. Also in this region loss of subcutaneous fat is very con-



Fig. 4



Fig. 5

incision. The shaded area indicates the extent to which the skin is undermined. The arrows indicate the direction of skin traction. *R*, skin resection in the frontal region.

siderable. The lines previously described are converted into accordion like folds forming the so-called colliers de Venus. Changes in the platysma muscle produce characteristic deformities. The platysma, which is a very important muscle esthetically, takes origin from the skin and subcutaneous tissue of the neck as well as from the fascia of the pectoral, deltoid and trapezius muscles and passes upwards to be inserted into the base of the mandible and the parotideo-masseteric fascia. It is frequently very intimately connected with the skin, lying superficial to the subcutaneous tissue. The muscle by its action produces ridges in the skin of the neck. These ridges are parallel in the submental region and spread out in a fan shaped manner in the region of the clavicle.

In old persons this muscle becomes fibrotic and shortened and the ridges

in the skin become permanent and can be seen as cord-life folds passing from the mandible to the region of the clavicle.

Prevention and Correction of Age Changes

Massage

The use of facial massage for the retardation of the development of lines and wrinkles is a practice to be recommended if suitable techniques are employed. It should be understood, however, that the procedure is only of value as a preventative measure and is completely ineffective in the presence of well developed wrinkles and furrows.

Nagera (19) has made a critical review of the various techniques suggested by the advocates of facial massage, particularly those of the French School. Massage of the face is directed toward the improvement of the circulation and trophism of the skin and subcutaneous tissue and also toward the prevention of atrophy and fibrosis of the facial muscles.

The most logical technique would appear to be that of Peytoureau (20). This author advises the following procedures.

1. Brisk stroking of the face, the strokes being in the direction of the muscle fibers.
2. Deep friction with one finger along the length of the muscle fibers.
3. Kneading of the facial tissue between the thumb and forefinger.
4. Sharp percussion with one or two fingers over the whole facial area.

It is advisable to carry out these procedures in the order indicated and to devote a two or three minute period to each one. It is not necessary to use creams when deep massage is being employed; a little vaseline or talcum powder is recommended as a lubricant. Before undertaking facial massage it is necessary to know the direction of the various muscle fibers. The areas which should receive special attention are the following:

1. Masseter muscle. The importance of this muscle in preserving facial contour has already been stressed.
2. Great zygomatic muscle
3. Orbicularis palpebrarum
4. Temporal region
5. Frontal region
6. Submental region
7. Orbicularis oris muscle
8. Neck region

Peytoureau insists that massage will merely impede the formation of wrinkles and can do nothing to erase them. Marfort (21), however, is of the opinion that precocious wrinkling or wrinkles in formation may yield to scientific massage. Sabouraud (22) advises against the massage of skin

which has undergone senile atrophy since manipulation of such skin merely results in still further stretching and an exaggeration of the wrinkles.

Recently the effect of the topical application of estrogenic substances to senile skin has received considerable attention. Max Goldzieher (7) and Joseph Goldzieher (23, 24) have studied the histological changes produced in senile skin by locally applied estrogens. They were able to demonstrate regeneration of atrophic epidermis with a marked increase in the number of cell layers and in the number of epidermal pegs. Some improvement was also noted in the collagen and elastic fibers of the cutis. Since it has been shown that degenerative changes occur precociously in the lined areas of the skin, application of estrogens to these areas may be beneficial in retarding wrinkling, Chieffi (25, 26) employing the method of Kirk and Kvorning described above has been able to show that inunction of the skin with estrogen in oil results in an improvement of the elastic properties of the skin. Since loss of skin resilience has been shown to be one of the factors responsible for facial ptosis, judicious use of estrogens may be recommended as a means of retarding its development. It has not as yet been determined by which mechanism the estrogens improve the elasticity of the skin but since the effect is demonstrable within a few weeks, it has been suggested that the improvement is due to changes in the structure of the ground substance. Gross (27), who has compared the skin of infants and of aged persons, has found that with age the fibrous elements of the intercellular substance are increased and the amorphous elements are reduced. Duran-Reynals (28) has shown that estrogenic stimulation of the skin of monkeys causes an accumulation of hyaluronic acid or its compounds and also results in an increased polymerization of these polysaccharides. Decreased permeability as indicated by the rate of spread of India ink has been reported by Sprunt (29) in estrogen treated skin.

Surgical correction of wrinkles and facial ptosis

It has already been stressed that the measures outlined above are directed towards delaying the onset of wrinkles and facial ptosis. When these conditions are fully developed, cosmetic surgery offers the only effective means of treatment. The operation of rhytidectomy is said to have been introduced by Gersuny in 1899. Later techniques were devised by Lexner (30), Hollander (31), Passot (17), Joseph (32) and others and modifications of their methods are still employed today. A detailed description of the surgical procedures is beyond the scope of this chapter and may be obtained from the publications of surgeons such as Claoué (18) and Brown (14). The principles underlying the surgical approach will be outlined briefly.

The aim of corrective operations on the senescent face is the elimination of wrinkles by traction on the skin and improvement of the ptosis by resection of redundant cutaneous tissue (fig. 5). For the purposes of rhytidectomy the face is divided in four areas:

1. Hair line to the glabella
2. Glabella to nasolabial line
3. Columella to inferior surface of the chin
4. Neck

All operations are carried out under local anesthesia with the patient in the upright position. The incisions are concealed in the hair line. The incision usually commences at the ear lobe. It is prolonged forward along the anterior edge of the auricle and upward to the hair line in the temporoparietal area and thence to the frontal region. From the lobe of the ear the incision is prolonged backward beneath the auricle to the posterior auricular sulcus and into the hair line above the level of the tragus. The skin is undermined for a considerable distance. In the frontal region it is undermined toward the glabella and in the temporal region towards the outer canthus. In the buccal region, the skin is freed from the underlying tissues for a distance reaching half way to the chin and along the body of the mandible. The skin of the neck is undermined for several inches along the sternocleidomastoid muscle. The undermining of the skin is performed superfically to the fascia and in this way the arteries, veins and nerves are protected.

Frontal ptosis is corrected by drawing the skin upward from the glabella to the hair line.

Elimination of "crow's feet" and improvement in the ptosis of the outer angle of the eye is obtained by lateral traction toward the temporal region.

The skin of the pendulous cheeks is drawn upward and rotated slightly back towards the anterior aspect of the auricle.

Double chin is eliminated by traction towards the lobe of the ear and the redundant skin of the neck is pulled upward towards the posterior auricular sulcus.

When sufficient traction has been exerted to eliminate the wrinkles and the ptosis, anchor sutures are applied to maintain the integument in the new position and the excess skin is trimmed away. Care must be exercised in order that the nasolabial sulcus be not entirely eliminated and the skin should not be so tightened that the resulting expression of the face is taut and fixed.

The two deformities which are not corrected by these procedures are the drooping of the upper eyelids and pouches below the eyes. These must be corrected by direct excision of crescent-shaped areas of the redundant skin. For the lower lid, the convexity of the crescent should be downward

and the line of closure near the lid margin so that it is covered by the lashes (33). In the upper lid the convexity of the crescent is upward and the line of closure at the upper extremity of the lid where it is hidden in the fold between the lid and the brow.

Finally, emphasis must be laid on the importance of the maxilla and mandible in maintaining normal facial contour. Since changes in these structures are responsible for much of the deformity of the senile face, every effort should be made to avoid or correct these changes. Hellman has shown that it is loss of teeth rather than ageing itself which causes shortening of the intermaxillary dimension, and Rogers and Applebaum (34) have demonstrated that proper intermaxillary dimension and the adult type of angle and ramus may be maintained by correctly fitted dentures or other restorations. Preservation of correct jaw alignment also prevents shortening of the muscles of mastication and preserves normal muscle tone.

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REHABILITATION FOR THE CHRONICALLY ILL AND AGED

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One of the most significant developments in medicine since the close of World War II has been the increased interest and emphasis which is being placed by medical schools, hospitals and physicians in physical medicine and rehabilitation. Although the physician has always been interested in the provision of any and all services which might provide for more complete medical care for his patients, it is only within recent years that the concept of total medical care has become an integral part of medical teaching and that hospitals, clinics and other medical care institutions have started to plan their facilities and programs in terms of making these services generally available on a broad scale.

This is well, for it is later than we think, and medicine's number one problem is no longer the acute communicable diseases which claimed their victims with dramatic swiftness, but is the slow and insidious processes of the chronic diseases and the disabilities which they leave in their wake.

To the physician the term "rehabilitation" has long connoted "the restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable." In general usage, however, the term itself, during the past few years, has lost much of its significance, for it has been used to describe everything from correctional programs in modern penal institutions to the social and economic rebuilding of war devastated countries. With the developing emphasis placed on the processes of restoring handicapped workers, a new term has arisen which describes such processes more aptly and with more virility. That term is "the third phase of medical care".

The modern concept of this third phase of medicine, which takes the patient from the bed to the job, springs both directly and indirectly from

the war. The rehabilitation programs of the military services and the Veterans Administration demonstrated that planned, integrated programs of convalescent care stressing activity as an adjunct to definitive treatment could reduce the period of hospitalization, offset the deconditioning phenomena of bed rest and prevent the harmful psychologic sequelae which often result from extended hospitalization. The technics of physical rehabilitation and retraining for the severely handicapped developed by the military services also have profound implications for the even larger number of our civilian population who are disabled.

Advances in Rehabilitation

Immediately following World War I, as today, there was a developing interest in increasing rehabilitation opportunities for the disabled. Unfortunately, this interest died in many quarters in the years between the wars. From it, however, did come some pioneer institutions and some needed legislation, such as the Federal Vocational Rehabilitation Act of 1920. The failure of the movement to gain sufficient stature to become an accepted part of medicine can be attributed to the fact that it was restricted largely to guidance, trade training and the purely vocational aspects of rehabilitation. Few provisions were made for physical restoration or reducing the physical disabilities of the trainees. When the physical condition became static, a program of vocational rehabilitation was planned, "training around" the disability rather than attempting to reduce or eliminate it through medical procedures. In many instances a comparatively large expenditure of time and money was necessary for vocational rehabilitation when, by the expenditure of a few weeks and a modest sum, the physical limitations could have been substantially reduced with an automatic increase in employment potentials. Such restrictions made it impossible for the state vocational rehabilitation programs operating under the Federal Office of Vocational Rehabilitation to give adequate service to their clients. Such failure is shown by the fact that until the basic philosophy of this program was changed by the Barden LaFollette Act of 1943, in twenty-three years only 210,000 persons were rehabilitated, although over 1,000,000 persons were in need of such aid at any given time during that period (1).

Although the underlying philosophy of the third phase of medical care is based on logic and common sense, basic and clinical research in medical rehabilitation has been minimal until the past few years. Studies done in the military services, the inquiries of Keys (2), Barr (3) and others into the deconditioning phenomena of bed rest, the numerous reports of Powers (4), Whipple (5), Dock (6), Menninger (7), Ghormley (8) and others on bed rest as it affects their particular specialties are indicative of an in-

creasing mass of scientific data on which such concepts are based. This evidence has been reinforced by the studies of successful experience with the impaired worker in industry, the economic values of rehabilitation as shown by the Office of Vocational Rehabilitation and the success of the Veterans Administration Physical Medicine Rehabilitation Program.

THE EXTENT OF DISABILITY

In thinking of the disabled, the average citizen is inclined to think of disabled veterans, yet the extent of physical disability among our civilian population is far greater. For example, the number of persons permanently disabled in farm accidents in 1945 was four times greater than the number of servicemen permanently disabled in the bloody assault on Iwo Jima. Ignoring the vast number of persons who suffer disabilities resulting from disease, each year in this country nearly 50 per cent more persons are permanently disabled from accidents alone than there were American servicemen disabled as a result of combat during the entire four years of the war. Added to thse are the 8,000,000 to 9,000,000 persons who suffer from disease of the heart and circulation, the 6,850,000 from rheumatism and arthritis, the 300,000 from cerebral palsy and a probable like number from the residual effects of poliomyelitis, the 1,000,000 known and additional 1,000,000 unknown cases of diabetes mellitus, the half million to one and one-half million persons with epilepsy, the 400,000 persons who have undergone major amputations, and the millions who suffer from disorders of vision, hearing and speech (9). These are the numbers, but they cannot tell the story of pain, anxiety, suffering and all of the difficult secondary problems that disease and disability leave in their wake. Aside from the pain and tearing personal and family anguish, the economic costs of disease and disability are staggering.

Until we find the etiology and treatment for the chronic diseases producing disability, we can expect, as the population ages, that the extent of physical disability in this nation will progressively increase. Since chronic disease is usually non-reportable, it is difficult to find reliable statistics on its extent. Although a census of such conditions has been proposed on several occasions, there has never been a complete survey of the extent of disability in this country. The most comprehensive source of information at present is the National Health Survey, conducted by the United States Public Health Service in 1935–1936. In this survey, 800,000 families in eighty-three cities and twenty-three rural areas of nineteen states were studied. The reliability of this study has been demonstrated in other selective samples on the extent of chronic disease and crippling conditions, and although results are not strictly comparable due to different methods of enumeration, they bear out the fact that the National Health Survey is

probably the best source available for such statistics, although later studies indicate that its results are probably conservative. It was this study that reported there were at that time some 23,000,000 persons in the United States who were handicapped to some extent by disease, accident, maladjustment or former wars. In a more recent study in New Haven conducted by the School of Public Health of the Yale University College of Medicine it was found that 121 persons for each 1,000 in the population suffered from chronic illness, and that one-third of this number were totally disabled and one-third below twenty-five years of age (10)

One of our great medical needs today is for the provision of total treatment of chronically ill patients in terms of the every-day problems of living which they face. Many such patients cannot be rehabilitated to the extent of employability, but a great percentage can be rehabilitated to the point of sufficient self-care so that they can live independent, dignified and happy lives at home, requiring a minimum of aid from other members of the family.

There was, at the war's end, some skepticism of the value of medical rehabilitation in the Veterans Administration hospitals for veterans of World War I, and those of the Regular Army who suffered from chronic illness and long-standing disabilities. Some physicians feared that young veterans of World War II would soon lose ambition, initiative and a desire for personal independence through association with older veterans who had developed "hospitalitis" as a result of boredom, frustration and hopelessness. In the veterans hospitals where comprehensive, dynamic rehabilitation programs are now in operation, the results have been not only revealing but encouraging.

Illustrative of the results obtained in the Veterans Administration is a study of 130 chronic neurologic patients in one hospital, all but two of whom were World War I veterans, and many of whom had not been out of bed in ten years. After nine months of rehabilitation, twenty-five had left the hospital and were employed; forty others had been discharged to their homes capable of light work, and, of those remaining, thirty were ambulatory and undergoing advanced rehabilitation, and twenty-five were capable of some self-care. All but 10 of the group had shown some worthwhile permanent improvement. With a five-year life expectancy of these patients, and a per patient day hospitalization cost of over $12, rehabilitation of this one group has saved the government and eventually the taxpayer, over $1,125,000. It would seem logical that a similar program for the civilian chronically ill would result in comparative savings.

In another study at the Veterans Administration Hospital at Manhattan Beach, Brooklyn, through rehabilitation, seventy-four of a group of 126 patients suffering from such diseases as arthritis, multiple sclerosis,

Buerger's, Parkinson's and heart disease and various forms of paralysis, have been discharged from the hospital and are now at home taking care of themselves. All but thirteen of the original 126 patients have recovered all or part of their ability for self-care. At the beginning of this study, eighty-three of these veterans were classified as "completely hopeless", but forty-nine of this group have been rehabilitated to the point of complete independence, and the remainder are capable of self-care.

The importance of dynamic therapeutics in the treatment of chronic illness in the Veterans Administration is readily apparent when we realize that the approximately twenty million veterans in this country represents a static population that is increasing in age daily. As pointed out in the Report of the Administrator of Veterans Affairs for the fiscal year 1948, there will be almost as many World War II veterans alive (3,800,000) at the turn of the century, 2000, as there were World War I veterans (3,727,000) in mid-1948 (11). The average age of the World War II veterans then, however, will be nearly 78 years, compared with an average in mid-1948 of less than fifty-five for World War I veterans, and seventy-two for Spanish-American War veterans.

Both the Veterans Administration and some civilian hospitals have demonstrated that rehabilitation to the point of self-care and even to full or limited employment is possible for many of the chronically ill who have been hospitalized for over long periods. Yet, in most of our civilian hospitals, the patient receives few services of this type. Hospitals complain that the chronically ill are responsible for their overcrowding, but they do little to provide the retraining services that will permit many patients to leave the hospital.

The hospital of today is being recognized more and more as the focal point in public health activities. With the changing demands being placed upon it because of the growing incidence of chronic disease and disability, it must also play a more important role in the rehabilitation of patients. Hospitals in the past have concentrated almost solely upon the definitive aspects of medicine and surgery. If the hospital is to meet the changing health needs of the public, it must assume greater responsibility for all three phases of health—prevention, definitive treatment and rehabilitation. As Bayne-Jones has said, "... they must become increasingly houses of prevention instead of houses of pity". For the problems of chronic disease can be met only by the creation and utilization of abilities, rather than merely the building of facilities.

Although it would seem logical that medical rehabilitation would be an important service in every civilian hospital, there has been little or no attempt, until, recently, to establish such programs in civilian hospitals. Of the 1,439,030 hospital beds in the United States in 1949, 33 per cent

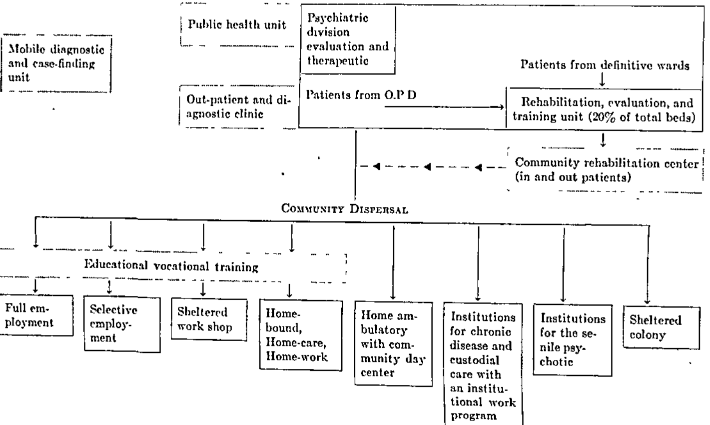
were in general hospitals, but these 574,683 beds cared for 92 per cent of all patients (12). Rehabilitation, in varying degrees, has been available in some tuberculosis, mental and other specialized hospitals, but little provision has been made for a dynamic rehabilitation program for the over 15,000,000 persons who are patients in general hospitals each year.

The Hospital Council of Greater New York has recommended that bed requirements for rehabilitation and convalescent care be placed at one bed per every one thousand population. This would mean that approximately 20 per cent of the beds in general hospitals would be utilized for this purpose. It was felt by the Council that the allocation of this number of beds and the introduction of a dynamic rehabilitation program would decrease hospital days, provide facilities for the evaluation and training of convalescent and chronically ill and disabled patients, and would help provide a program of total medical care.

Medical examination, x-ray and the usual hospital routines are not enough to meet the problems of the disabled persons. A diversified but integrated program must be developed for such patients on the basis of their needs in meeting day-to-day life situations. They must be provided with a program for training to teach them to utilize their residual abilities to the maximum. Patients must be tested and then trained in the activities of daily living; the simple things, such as turning over in bed, dressing and undressing, applying and removing braces, getting from the bed to the wheelchair or the standing position. These are every-day things, but they are the foundation of self-care and physical independence.

Hospital programs alone, however, are not enough If we are to meet the needs of the disabled, chronically ill and aged, we must have a broad community program of dispersal after discharge from the hospital. The hospital, of course, is the focal point, the sorting station and the training ground, for just as satisfactory job placement is the capstone of any successful program of services to the handicapped, medical rehabilitation, starting at the earliest possible moment following acute illness or injury is the foundation, for all subsequent rehabilitation processes are built upon the residual physical disability which medical services cannot eliminate (fig. 1).

The end of rehabilitation for some patients leaving the hospital is *full employment*, for in many instances the disability can be eliminated or the patient can be rehabilitated to the point that he is not vocationally handicapped. An example of such cases is that of a miner recently sent to New York for rehabilitation under the auspices of the Welfare and Retirement Fund of the United Mine Workers of America. For five years this patient had had a total paralysis of one of the upper extremities which came on after an injury in the mines. The nerve had healed completely, but during



Rehabilition Program in the Total Community Program for the Chronically Ill
The Community General Hospital
Mobile diagnostic and case-finding unit
Public health unit
Out-patient and diagnostic clinic
Psychiatric division evaluation and therapeutic
Patients from O.P D
Patients from definitive wards
Rehabilitation, evaluation, and training unit (20% of total beds)
Community rehabilitation center (in and out patients)
Community Dispersal
Educational vocational training
Full employment
Selective employment
Sheltered work shop
Home-bound, Home-care, Home-work
Home ambulatory with community day center
Institutions for chronic disease and custodial care with an institutional work program
Institutions for the senile psychotic
Sheltered colony

Fig. 1

the long healing process, the arm had become alienated. Electrical stimulation demonstrated to him that the hand was functional. After three days of therapy, the patient had a 90 per cent return of function and only needed continuing treatment to restore the atrophied muscles to their normal strength, in order to return to his old job.

The great majority of those patients who are permanently disabled are not vocationally handicapped if *selective placement procedures are used*, in which an analysis is made of the physical capacities of the individual and they are matched to the physical demands of the job. Just as there are powerful forces of physiological compensation in the case of disease or injury, it is possible, through retraining, for the remaining physical capacities of the disabled individual to be utilized vocationally With the paraplegic patient placed in a position which requires strength in the muscles of the shoulder girdle and upper extremities, the blind person in a position which requires finger dexterity and aural acuity rather than vision, and the deaf person in a working atmosphere of noise and confusion, objective studies have shown they are far more reliable, efficient and safe employees than the able-bodied.

For those persons whose physical disabilities are so great that they cannot work in normal industry even with selective placement, we must have a series of *sheltered workshops*. Throughout the nation, we have a number of pioneer institutions such as the Institute for the Crippled and Disabled, the Cleveland Rehabilitation Center, the Goodwill Industries, and others who have demonstrated the physical, psychological and social values of permitting any person regardless of the severity of his disability to gain dignity which comes from productivity.

For those persons whose disabilities will not permit them to travel to and from a sheltered environment, we must provide programs of *home care, housekeeping services, and industrial homework*. As demonstrated by Jensen's work at Rochester, similar programs in Syracuse, and the outstanding program developed by Bluestone and his associates at Montefiore Hospital here in New York, the provision of home medical care programs supplemented by adequate social service and visiting housekeeping service can reduce the financial and professional strain upon our hospitals and give the patient a more satisfying life within the family environment. Added to this there should be a program of industrial home work both for the monetary and psychological benefits it can bring to patients.

One of our most neglected groups in the chronic degenerative disease category of patients has been the *senile psychotics*. They have usually been placed in the almshouse or county institution along with individuals of all ages and of normal mentality, or have been sent to state institutions for

the insane where often, because of the crowded conditions, they have been placed with severely disturbed psychotics.

How a community can meet the needs of this particular group has been demonstrated in Vancouver, B. C., where a number of small, standardized, economically-built 100 bed units for their care have been placed in centers of population. The doctors in each community have assumed the medical responsibility, and mature, motherly-type practical nurses have been selected for patient care. Such units, strategically placed, allow the patient to maintain contact with his former environment and have visits with his old friends and family. Through such plans, optimum results may be obtained at minimum cost.

In our failure to utilize "work therapy" with institutional patients suffering from chronic disease and physical disability, we have neglected one of the most valuable tools in the management of this group of patients. All who have gone through a custodial institution have noted the apathy and hopelessness of most residents. There are always a few however, who are bright and active. They are the patients who have volunteered or have been assigned to tasks within their phsycial capacities.

The use of selective placement can be used in such institutions as well as in industry. Even though their capacities may be limited, the great majority of the residents of public homes can do some tasks about the home. For some it may be only simple housekeeping assistance; others may have the ability and experience to assume greater responsibilities. Such jobs should carry regular compensation, even though it be small, for there is no greater satisfaction than that which comes through earning. In many homes, it would be possible to provide sheltered workshop facilities where residents could do either industrial home work or necessary services for the community operating the home. Like work for the homebound, such plans require both imagination and close supervision to prevent exploitation, but they would pay tremendous dividends by providing a purpose in life for many patients.

With the introduction of rehabilitation programs in general hospitals, increased facilities for convalescent care and home care programs of medical, social, visiting nurse and visiting housekeeping services, many of the aged and chronically ill will not need to seek admittance to public homes. Many present residents could be restored either to employment, selective placement, sheltered workshop, employment, or self-care within the home. But in order to accomplish this, there must be a complete program for evaluation and training within the hospital.

Age plus physical disability will prevent many chronically ill persons from returning to employment. Vocational placement, however, is not the only valid goal of rehabilitation. The factors of self-care and ability to do

productive work while still living in a hospital, home or other institution are also valid objectives. They are valid medically and socially for their effect on the well-being of the person, and economically, in that personnel and operating costs of the institutions or the patient's home are thereby reduced.

The Doctor's Responsibility

The practice of rehabilitation begins with the belief in the basic philosophy that the doctor's responsibility does not end when the acute illness is ended or surgery is completed; it ends only when the patient is retrained to live and work with what he has left. This basic concept of the doctor's responsibility can be achieved only if rehabilitation is an integral part of medical care. Rehabilitation is only as sound as the basic medical service of which it is a part. The diagnosis and prognosis must be accurate, for it is upon them that the feasibility of retraining is determined.

In addition to the general diagnostic studies, the medical evaluation of the orthopedically handicapped must include muscle tests, determination of joint range of motion, and tests for the inherent needs in daily living In the rehabilitation service at Bellevue Hospital, a check list of ninety-six items is used to determine these factors (chart 1). They include: 1) bed activities, such as moving from place to place in bed, and the ability to sit erect; 2) toilet activities; 3) eating and drinking; 4) the ability to dress and undress, such as tying shoe laces, manipulating buttons, zippers, and other fasteners, and applying and removing braces, 5) hand activities—for example, winding a watch, striking a match, and using various door knobs, and latches; 7) wheel chair activities, getting from the bed to the wheel chair, the wheel chair to bed, and in and out of the bathtub, and 8) elevation activities, which include the needed abilities for walking, climbing, and traveling.

The tests may be administered by a therapist, a well-trained volunteer, or even a member of the patient's family. From the special check sheets used for charting the patient's accomplishments, information is readily available both on the status of the patient at the time of admittance and his progress while undergoing rehabilitation.

In Bellevue and Goldwater Hospitals and the Institute of Physical Medicine and Rehabilitation, after the basic medical work-up and the range of motion, muscle, and needs of daily living tests, the physician, in conference with other staff members, prescribed a five-hour-a-day program for the patient. These prescribed activities include training in the ambulation and elevation rooms and the remedial gymnasium, occupational therapy, physical therapy, speech therapy, or any other activity which may be helpful in meeting the specific needs of the patient.

CHART 1—*Continued*

	Grade	Date		Grade	Date
Walking activities (continued) K 1 Cross standard street on green light—40 seconds			5. Pick up object from floor		
			6 Carry cafeteria tray with dishes	•	
2 Get in, out of bus, use turnstile—20 seconds			Total non-walking (49)		
			Total walking (29)		
3 Erect position to car			TOTAL ALL ACTIVITIES (78)		
4 Car to erect position			THERAPIST.		

In a comprehensive rehabilitation program, vocational guidance specialists should also be available to do guidance and testing, in order that the patient may be started on a prevocational exploratory and work-testing program as soon as it is medically feasible. However, good basic rehabilitation can be carried out with the personnel available in the ordinary general hospital, if such a program is properly organized, supervised, and prescribed by the physician.

PROBLEMS OF THE HEMIPLEGIC

Today, more and more of a physician's practice consists of physical disabilities resulting from chronic disease, and of this group there is no single clinical entity of the magnitude of hemiplegia. Today, on the basis of earlier statistics, it is estimated that there are over 1,000,000 hemiplegic patients in the United States.

Medically, we have been interested in the hemiplegic patient during the acute phase of his illness and then forgotten him if he survived. Many of these patients are capable of learning to care for themselves and to walk again, but unfortunately, it has usually been left to the individual or to the family to provide the help the patient needs to return to an independent life.

A review of the neurologic pathology of patients with apoplexy reveals that it may be caused by thrombosis, hemorrhage or embolism. These are listed in the order of frequency of occurrence. Spasm of the cerebral vessels may be a fourth cause and would explain the transitory hemiplegia occasionally seen.

There are two clinical manifestations of apoplexy, the first being the

acute or general. The most common symptom of the acute manifestation is the disturbance of consciousness, resulting in stupor or coma. The second manifestation is the local or focal signs of apoplexy, which reflect immediately in the loss of function of the particular part of the brain affected. This is, of course, the hemiplegia or paralysis.

The causes of cerebral hemorrhage may be listed as follows: arteriosclerotic vascular changes of the cerebral vessels; syphilis of the cerebral vessels; intoxications, such as those from lead and alcohol, and infectious diseases.

In itself, hypertension is not sufficient to cause hemorrhage into the brain without nephritic changes and cerebral arteriosclerosis It is known that continued hypertension eventually leads to an enlarged heart and cerebrovascular disease.

Embolism, the second cause of apoplexy, is most frequently the result of dislodgment of a vegetative embolus from the valves of the heart after rheumatic heart disease. Emboli also may be dislodged from the wall of the pulmonary vein or aorta.

Cerebral thrombosis is generally due to pathologic alterations in the walls of the cerebral vessels or to changes in the rate and flow of the blood. Thrombosis is more common in cerebral arteriosclerosis or in any other condition in which the interior of the artery undergoes atheromatous conditions. Thrombotic occlusion is most common in patients past middle life and those of advanced age.

Infectious diseases, such as diphtheria and typhoid fever, may cause changes in a vessel wall, forming a favorable site of thrombosis.

No part of the brain is exempt from damage from thrombosis, hemorrhage or embolism. However, the favorite sites of hemorrhage are the lenticulostriate and lenticuloopic arteries. When these vessles rupture, there is involvement of the cerebral or basal ganglions and predominant involvement of the internal and external capsules and of the thalamus and striate bodies Emboli are found in the terminal arteries and also in the bi-furcations of the larger arteries such as the carotid and vertebral, and these, in turn, may serve as the starting point for thrombosis.

As with all patients who seek rehabilitation, it is necessary to select only those for whom something can be done. One must exclude cases in which the rehabilitation cannot keep up with the pathologic processes as seen in the patient with malignant hypertension or encephalomalacia or advanced senility. Rehabilitation may be started with patients with hypertension if it is believed that they can stand a trial period of activity. Such patients should be closely supervised and should have adequate rest periods to avoid fatigue. It has even been found that some patients have had a drop in blood pressure under a regimen of mild activity. All hemiplegic

patients undergoing rehabilitation measures should be checked at least twice weekly for blood pressure, pulse rate and general clinical condition.

In addition to being in sufficiently good physical condition to justify the effort, the patient himself must have the will power and motivation to carry out the rehabilitation program, which, of necessity in many cases, may be fairly strenuous and may extend over a fairly long period.

Careful evaluation must be made of the mental and physical status of the patient with hemiplegia. Before rehabilitation is begun a psychologist, or even a psychiatrist if necessary, should determine the patient's ability to learn simple procedures, such as tying his tie and dressing himself. Some hemiplegic patients are not able to retain instructions given a day or even a hour previously. When the learning ability is affected to this extent, rehabilitation is not feasible.

The patient who is accepted for rehabilitation is first given a careful physical examination. A muscle test is then given to determine the power of both the affected and unaffected muscles. Range of motion of joints is checked and noted. He also is given the activities of daily living test, which consists of 102 items. Each item measures one activity—such as the patient's ability to move from place to place in bed, to get from the bed to the wheel chair and back to the bed, dressing and undressing himself and combing his hair. The activities that the patient can carry out at the time of the first examination are marked in black; the unfilled blanks indicate the activities that he must learn to perform if he is to return to an independent life.

Two simple tests will reveal whether the hemiplegic patient will be able to walk again. If he can move the arm on the affected side freely, there is every reason to believe he will be able to walk since the arm is usually more affected than the leg on the paralyzed side. If he can raise the affected leg an inch or two off the sheets while in a supine position, there should be sufficient muscle power remaining to permit him to walk again.

Rehabilitation should be instituted early in the course of the illness. There should be no untoward results if the patient whose apoplexy has been caused by thrombosis or embolism starts on bed activities *twenty-four hours* after regaining consciousness. In cases in which *hemorrhage* has been the cause, the patient is kept on bed activities alone for the first three weeks and then is allowed to sit up in bed and start other simple procedures of active training.

Disabilities that result from a cerebral accident are limitation of motion of the joints on the affected side and a spastic or flaccid paralysis. There may be a facial paralysis, and if the paralysis occurs in the dominant arm the patient will usually have a sensory and motor aphasia.

Regarding evaluation of the disabilities, if treatment is started early

there will be no limitation of motion at the joints, and the affected arm and leg can be passively moved through their normal range. If, however, rehabilitation is not begun soon enough, contractures usually result, especially at the shoulder.

A flaccid hemiplegia only occurs in a small percentage of patients. The usual spastic hemiplegia presents the following signs:

The affected *arm* is internally rotated and adducted, and the forearm, wrist and fingers are flexed. When the patient is asked to move the affected arm, he will elevate the shoulder and abduct and internally rotate the arm. When the *leg* is fully extended voluntary dorsiflexion of the foot is impossible. When, however, the knee is flexed and the patient flexes his hip against resistance, the foot will dorsiflex and supinate (Strümpell's phenomenon).

Some patients may have an angiospasm of the cerebral vessels and present a typical hemiplegic syndrome. There is usually a complete return of function in a few days. If a patient has a normal return of function in the upper extremity, the lower extremity will usually be found to be normal.

In the early stages of treatment, the following procedures should be instituted to prevent deformities: footboard or posterior leg splint to prevent foot drop; sandbags to prevent outward rotation of the affected leg; a pillow in the axilla to prevent adduction of the shoulder; and quadriceps-setting exercises to maintain muscle strength. All these procedures are relatively simple and require no special equipment. Their use, however, will prevent crippling anatomic deformities and hasten rehabilitation.

The next procedure indicated is the institution of pulley therapy. This can be done very simply with a small pulley attached to a goose-neck pipe over the head of the bed, the ordinary clothes-line rope with a 1-inch webbing for the hand loop being used. With the stretching and passive exercise provided by pulley therapy, the range of motion can be increased, and adhesions prevented (fig. 2).

Pulley therapy has the advantage over the usual stretching exercises that are done passively, for the patient, knowing his own pain threshold, will proceed to fully tolerated motion much more quickly. Pulley therapy can also be used to aid in the re-establishment of reciprocal motion patterns.

The patient, at this stage, should be encouraged to sit erect in order to re-establish balance. Speech therapy, if indicated, should be instituted at this time. In the absence of a trained speech therapist, the speech re-education can be started under medical supervision by any teacher who has had some experience in this field. It is well for the physician to point out to the aphasic patient and his family the nature of the condition in order

that the inability to use the tools of language may not be interpreted as loss or diminishing of the ability to think and reason.



Fig. 2

The next progressive stage in retraining the hemiplegic patient is ambulation, which should be started by the practice of balance in the standing position, progressing to the parallel bars; the teaching of a heel-and-toe gait to minimize clonus and to re-establish normal walking habits stressing reciprocal motion; and a short leg brace (needed in approximately half the

cases) to correct foot drop. All the equipment for training in ambulation is simple and readily obtained by the general practitioner. If parallel bars are not available, two kitchen chairs may be used.



Fig 3

Approximately 50 per cent of hemiplegic patients need short leg braces to correct the toe drop frequently seen with this disability (fig. 3). The double-bar short leg brace with a 90 degree stop is used in the majority of cases. In less severe cases, the patient may be fitted with a spring type of brace, which extends from the heel of the shoe up the posterior aspect of

the leg to the calf. For cosmetic reasons this brace is preferred by many patients.

As the patient progresses with his ambulation, he is taught to climb stairs and curbs, and how to get into a bus or automobile.

In the advanced stages of retraining, ambulation is continued with instruction in crutch walking, starting usually with the alternate four-point gait, and teaching of elevation, with stress on climbing steps, curbs, stairs and ramps. Concurrently with training in ambulation, attention should be given to retraining in the activities of self-care and daily living.

A right hemiplegia in a right-handed person is a serious disability because of the sensory and motor aphasia and the lack of skill in the left hand to perform the activities essential for daily living. The training of the left hand should be started early, since the patient must become left handed if he ever hopes to care for his daily needs. Simple tasks in eating and dressing should be started. Left-hand writing must be practiced, for this is an important means of communication, especially when speech is affected.

Training of the affected arm is started while the patient is developing one-handed skills with the unaffected arm. If the arm is flaccid, a re-education program similar to that used in poliomyelitis should be started. Many of these patients have a complete return of function if muscle re-education is carefully given over a long period. The rehabilitation of the spastic arm should start at the shoulder. The most difficult shoulder movement for the patient to regain is external rotation. Flexion and extension of the forearm are difficult for the patient with spastic hemiplegia to perform. When asked to flex the elbow, he elevates the shoulder and abducts and internally rotates the arm. Pronation and supination of the hand are usually impossible, since these are the last movements learned by man and the last to return. Internal and external rotation of the arm are primitive movements, and the patient attempts to substitute these movements for pronation and supination. The fingers and thumb are usually flexed tightly; if they are forced open they can be flexed but active extension movements are usually impossible. On yawning the fingers of the hand usually extend.

The fingers of the patient with spastic hemiplegia usually cannot be re-educated for any useful purpose. If adequate function is attained, it will take years of effort by the patient. In the aged person with cardiovascular disease it is not often worth the effort. One should not, however, have the patient give up hope of ever using the fingers. He must be made to understand that movements of the fingers depend upon the proper functioning of the shoulder, elbow and hand and placing the hand in positions for purposeful movements.

Obviously, the physician himself cannot undertake the actual administration of the retraining, but the therapist, nurse, volunteer or even a

member of the family can conduct the activities under his supervision. With such a program, many of the complications that usually follow apoplexy can be avoided, and a great deal of ability salvaged.

Problems of the Amputee

Although the geriatrician is often forced to call upon the services of the surgeon and the specialist in peripheral vascular diseases when dealing with amputee patients, he must assume the responsibility for preparing his patient physically and psychologically for the amputation and must see that the patient has the proper prosthetic device, adequately fitted, and is trained in its use.

One phase of the management of the amputee to which the physician should give particular attention is the immediate postoperative period while the stump is being shrunk in preparation for prosthesis and fitting. It is during this period that contractures may occur from muscle imbalance, faulty posture, placing the stump on a pillow, or prolonged sitting or plaster casts.

Among the most common of these anatomic deformities is hip flexion which may occur from elevating the stump on a pillow while lying in bed or from prolonged sitting in a wheelchair. Such a flexion deformity may take from six to eight weeks of arduous, painful work before sufficient hyperextension can be regained for satisfactory walking. It can easily be prevented by keeping the A-K amputee on his face for several hours a day and prescribing extension exercises either with or without heavy resistance.

In advising his patient on the selection of a prosthetic device, the physician must be aware of the fact that not all limbs are suitable for all amputees. In fact, he must realize that not all amputees can wear artificial limbs profitably. It is a common misconception that if a proper fitting limb is made, the patient need only put it on and walk away. We have noted that an above-knee amputee in the older-age group cannot, as a rule, profitably be trained to use a prosthesis if he is unable to perform a swing-through gait on crutches. If a prosthesis is denied a patient, the reasons must be carefully and thoroughly explained to him, for psychic trauma from denial is not uncommon.

The physician must point out objectively those skills which the patient can expect to achieve with proper training and those skills which the pa-
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quate training. Training is absolutely essential if the amputee is to be successfully rehabilitated.

Multiple Sclerosis

Because of the hopeless outlook in multiple sclerosis, therapy has in general been directed toward symptomatic relief, and the approach has been a negative one. In rehabilitation, the disability, rather than the specific disease process which has produced it, is our primary consideration. In multiple sclerosis, the problems are the same as in any other chronic, progressive, crippling disease. In considering the feasibility of successful training of a patient, progression of the disease must be carefully evaluated; if the disease process outstrips training, such training is obviously wasted.

The primary consideration in working out a program for rehabilitating the severely disabled is to teach him to live and, if possible, to work, with what he has left. Those capacities can be determined only through performance testing. It is impossible, through the analysis of the clinical manifestations of a disease such as multiple sclerosis, to determine what the sum total of the remaining physical capacities of the patient can be trained to do in the way of work or self-care activities. In addition to general diagnostic studies, the medical evaluation of the patient with multiple sclerosis must include muscle tests, joint range of motion tests, and tests for the inherent needs of daily living. These are of primary importance, for it is on their results that the patient's rehabilitation program is planned.

Too frequently, in rehabilitation, many of the basic skills necessary for effective daily living are overlooked. The patient is given numerous medical, psychologic, and vocational services in preparation for employment; but retraining in the basic physical skills of ambulation, elevation, and self-care activities is neglected, with the result that the patient, being unable to walk, travel, or care for his personal needs, is also unable effectively to utilize the other medical, psychologic, social, and vocational services which he has received for richer and fuller living.

Retraining in the basic physical skills of daily living is primary; it is simply a matter of "first things first", for daily activity skills are the basis for all subsequent rehabilitation processes.

It has been found difficult in many instances to differentiate between muscular inability due to disease and that due to atrophy of disuse; and sometimes only a test period of conditioning exercise will provide this information, which is vital in the training program.

From the information gained by the tests for the factors of daily living, a suitable program is set up for the patient, designed to meet his particular needs. It has been noted, especially in hand activities and gait training, that persons long incapacitated from multiple sclerosis will have alienation and overcompensation of certain muscle groups. With muscle re-education

and definitive therapeutic exercise, much may often be accomplished in correcting these conditions.

Problems of the Paraplegic

Among the most difficult problems which the physician faces in rehabilitation are those presented by paraplegic and quadriplegic patients.

Although the rehabilitation of these patients is a mission requiring the teamwork of the orthopedist, the neurosurgeon, the urologist, the neurologist, and in many instances the plastic surgeon, it is a rehabilitation problem in which the general practitioner plays an important role His services are invaluable in maintaining the morale, nutrition, and general health of the patient, and on his shoulders frequently falls the task of correlating the work of the specialists and interpreting it to the patient In many instances, he must also make the decision as to whether rehabilitation should be attempted. This decision is one that should be approached with hope, courage, and understanding, rather than the defeatist attitude that so frequently exists.

There are a few basic rules in the management of the paraplegic that are fundamental. First, it is most unwise to attempt immediate manipulation. Hoen has reported three cases during the war in which the individuals obviously did not have a transected cord until the ambulance attendants posturing them by the rule book in hyperextension, evidently severed the cord with this manipulation. He described most graphically the case of a young naval aviator who had made a crash landing The patient had a severe pain in the back, but had sensation and motion in both lower extremities up until the time he was picked up by the ambulance crew. They immediately postured him in hyperextension, and before he arrived at the hospital, there was no sensation or motion in the lower extremities; obviously his cord had been severed during the trip. The rule should be: do not manipulate or posture until you know the type of lesion.

Whenever there is any question of the extent of injury, early exploratory laminectomy is indicated, not only to relieve pressure, but in some instances to save the traumatized cord. It is important also that if transection is actually observed surgically, the patient can be told factually as early as possible what he faces. The patient will usually accept his condition and rehabilitation will be greatly facilitated by his early cooperation and work, rather than "waiting for a miracle".

The management of the bladder is most important. Tidal drainage is the simplest method of early management. However, this may not be feasible, and a certain percentage of cases will require suprapubic cystotomy.

One of the greatest problems in the management of paraplegia is the

prevention of decubitus ulcers. Frequent turning and good nursing are most valuable, but it is all important to maintain a high protein intake from the onset of the condition. If this is not possible by the usual dietary supplements, amino acid, blood transfusion, and all of the other means available should be exercised.

It is now a well-established fact that nutrition plays a primary role both in the development and the healing of decubiti. In certain types of patients, these will develop within 24 hours after the injury if strenuous methods are not followed to prevent them.

It is important to start bed exercise very early, especially to strengthen the triceps and finger flexors. Most hospital management routines include a trapeze or monkey bar to facilitate movement. This does nothing to develop the triceps; in fact, because gravity pulls the patient down, there is often a disuse atrophy of the triceps. Simple exercises to strengthen the muscle groups needed for adequate crutch walking should be routinely prescribed.

Paraplegia is not the hopeless condition it was once felt to be. There were some 400 paraplegics as a result of World War I, and only one is alive today. Of the 2,500 paraplegics of World War II, some 80 per cent are living useful lives on a combined brace-crutch-wheel chair existence, and a large per cent of these are either in school or in jobs. In a recent personal experience with 130 paraplegic miners sent to the Institute of Physical Medicine and Rehabilitation with the paraplegia existing from 3 months to 19 years, 100 were retrained to the point where they were capable of a program of continued vocational training for work on a selective placement basis or were able to return to some gainful work in the mining industry.

Problems of the Quadriplegic

Quadriplegia, in the past, has been considered one of the most difficult and hopeless problems in medicine. Today, this is not true.

In the rehabilitation of the quadriplegic patient, it is of prime importance that he be seen early in order that spasticity and other contributing causes to contractures may be controlled. The status of bowel, bladder, decubitus ulceration, and general paresis of the trunk and abdomen must be appraised in terms of their severity and amenability to correction before rehabilitation is considered.

The management of the quadriplegic patient is twofold; it lies in the measures directed toward preparing the patient for rehabilitation, and in the rehabilitation training program.

The measures are:

1. Prevention of deformities or contractures (a) by the judicious use of

splints (plaster of Paris, plastic, footboards, and sandbags), and (b) by a planned procedure for passive motion by a therapist or nurse to all movable *joints.*

2. Exercises: At the earliest permissible time, active and passive exercises should be begun to prevent atrophy of disuse, to maintain or improve muscle strength, and to prevent the deconditioning phenomenon of bed rest. Particular efforts should be extended toward maintaining strength in the arm and hand muscles. Reverse push-up (pushing sandbags or dumbbells) are of particular benefit. Breathing exercises to maintain normal aeration, to correct reverse breathing and to establish new breathing patterns are likewise necessary.

3. Care of the skin: The management of decubitus ulcers may be considered as twofold, prophylactic and therapeutic The usual prophylactic measures are frequent turning and keeping the bedclothes and patient dry. The necessity for maintenance of general nutrition and the necessity for protein supplementation directed toward maintaining normal blood-protein levels as well as vitamin supplementation are obvious. The full thickness skin graft for the closure of large decubitus ulcers has been the most effective measure in this group.

4. Bowel and bladder training: Measures should be undertaken for regulation of sphincter impairment as soon as feasible. Evaluation of the bladder status should be made as indicated. A catheter should never be left in the urethra for more than five days without being changed, as calculi formation around the catheter tip often occurs. Routine urinalyses should be performed in order to insure the early treatment of urinary infections. As soon as possible, the patient should be placed on a rigid twenty-four hour training schedule starting with one-half hour intervals for voiding, and the intervals should be increased to individual tolerance. The management of the bowels usually resolves itself to one of constipation which can be controlled through the use of bulk-forming foods, and enemas or glycerin suppositories as necessary.

5. *Prevention of cardiovascular and respiratory deconditioning:* All patients are likely to exhibit a blackout, syncope-like phenomenon when the first attempts to sit up are made. Since the work of Dietrick and his associates demonstrated the hyperreaction to the tilt-top table after prolonged bed rest, it seems obvious that semirecumbent posture for at least part of the day is indicated. After prolonged bed rest, the patient should be kept in the sitting position for only a few seconds the first day, and thereafter the intervals should be gradually increased to full tolerance.

On the basis of the total evaluation data, the patient is placed on a five-hour training program. Physical therapy, in the form of heat, is usually used prior to any exercise session, particularly if any pain or

spasticity is present. Hydrogynmastics, electric stimulation of muscles, and ultra violet radiation are all valuable. Occupational therapy is prescribed for both its psychologic and specific physiologic and functional values. Such activities as would require hand and arm motions are obviously beneficial to these patients. Special training routines are instituted to teach the patient how to roll from side to side in bed and how to sit up in bed. Mat exercises, push-ups on the mat, wall pulleys, and similar exercises are added at opportune times in an effort to improve the strength of the upper part of the body. Periodic muscle tests are done to evaluate the degree of return of muscle power.

Accurate prognosis in quadriplegic patients can be made only after a preliminary period of six weeks of rehabilitation training. After this period and a re-evaluation of the status of the patient, noting return of motor power, the psychologic attitude toward his disability and the social and vocational problem, a long-range program may be outlined. It has been found that the full utilization of the patient's waking hours in any form of activity, using occupational therapy and recreational therapy, makes for a more cooperative patient. Activity alleviates anxiety. The success or failure of any rehabilitation program rests with the patient's attitude toward his disability, and this cannot be overemphasized in the case of quadriplegic patients. Time spent with the patient and the family in discussing the problem with which they are faced in invaluable for future orientation and planning.

With the growing increase in chronic disability resulting primarily from an ageing population, medical care cannot be considered complete until the patient has been trained to live and to work with what he has left. Rehabilitation is a medical responsibility.

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CANCER AND AGEING

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Many conflicting observations or opinions complicate the relationship of cancer to ageing. It is common experience that human cancer occurs in greatest frequency in advanced age; yet it is often stated that if an individual lives long enough, he will not develop a cancer. Furthermore, the types of cancer which occur in young persons generally tend to be of a more malignant order, and the course of cancer is usually shorter in the young than in the old. The problems stemming from these observations may be formulated in the following questions.

1. Do the processes of ageing favor the development of cancer?
2. What is known about the causation of cancer which would relate the disease to old age?
3. Is the incidence of cancer a direct and continuous function of age?
4. Is the behavior of cancer modified by the age of the host?

Much of the difficulty of relating cancer to age results from including all varieties of malignant growths in a single category. While it is obvious that all types of cancer have sufficient characteristics in common to set them apart as a major type of disease, to be distinguished from inflammatory or degenerative diseases, information regarding the relation of cancer to age can perhaps be obtained only in the case of specific types of cancer which have a frequency within a species great enough to be predictable under certain conditions and perhaps are capable of statistical evaluation. Attention must therefore be directed largely to specific types of cancers, whether spontaneous, induced or transmitted, in order to analyze the relation of cancer to ageing. A complete analysis is not possible in this chapter; but it is hoped that the references cited, admittedly incomplete and perhaps prejudiced in selection by the author's interest, will form a starting point for those who would study the subject in more detail than

is presented here. What is known about the relation of cancer to ageing is perhaps applicable also to benign tumors, although in general the slower growth, longer silent period and lower degree of autonomy of the latter present greater obstacles to analysis.

Do the Processes of Ageing Favor the Development of Cancer?

There is no single yardstick by which the processes of ageing can be measured. Each animal species, with advancing age, exhibits a pattern of disease seemingly characteristic of the species and seemingly dependent upon the structure and functions of the organs involved. According to frequency and severity, these diseases become the factors determining the life span. That underlying changes of ageing may govern the time of expression of the diseases and their intensity cannot be doubted. Nevertheless, it is extremely difficult, if not impossible, to distinguish ageing from disease, particularly when the latter is well advanced. Furthermore, as Loeb (1) has pointed out, ageing processes as such are injurious and often resemble diseases. The most comprehensive consideration of the relation of cancer to processes of ageing was published by Loeb in 1945 (2), and the interested reader should consult this article. Ageing of higher organisms is characterized by a decrease of mass, function and growth energy of the parenchyma, together with an increase in mass and density of the intercellular stroma. Such processes would seem unfavorable to the development of cancer. Nevertheless, the metabolic, functional and growth processes of the organism occur largely in the form of cyclic rhythms superimposed upon the continuously declining time curves of the individual and his constituent parts. These basic cyclic functions become less perfect with advancing age and are also influenced by external stimuli. The incompleteness of cyclic response of tissues to growth stimuli may ultimately lead to a permanent and irreversible increase in growth energy. According to Loeb (2), cancer occurs with increasing frequency in later life largely because long continued stimuli are required to produce this type of growth. It may be that the increasing density and hyalinization of stroma as well as atrophy of epithelium would favor cancer formation indirectly by causing the tissues to be more vulnerable and by prolonging the regenerative phase following injury (2). However, the declining growth energy of the tissues generally associated with ageing is not entirely offset by variations in basic cyclic functions, whatever their cause. If this were so, the incidence of cancer would approach a linear function with advancing age, other things being equal. We have no direct evidence that pure ageing processes, if such there be, independently favor the development of cancer.

The occurrence of cancer in certain individuals but not in others subjected to the same stimuli can only be explained by the genetic makeup of the

individuals. It is beyond the scope of this chapter to discuss the abundant clinical and experimental evidence of the hereditary component of cancer formation, which is thoroughly reviewed in many text books of general and special pathology (3), other than to recall the equation $H \times S = C$, applied by Loeb, Burns, Suntzeff and Moskop (4) to mammary carcinoma in mice. The strength of genetic factors times the intensity of stimuli may determine not only the frequency of so-called spontaneous mammary cancer in mice, but also largely the age at which it appears. There is evidence that this equation may be applied in some way to many if not all cancers, and that the genetic component is indispensable to cancer formation. In experimental studies using inbred strains of animals, the genetic factors may be kept fairly constant so that the influence of other factors, including age, on cancer growth may be evaluated. When this is done, as discussed below, the preponderance of evidence is against the thesis that ageing as such enhances cancer development.

If the processes of ageing favored the development of cancer, it would be expected that cancer could more readily be induced in old than in young animals. Much evidence has been accumulated as to the role of estrogen in the genesis of mammary cancers of mice (5). Nevertheless, experiments, notably by Loeb, Suntzeff, Burns and Schenken (6) and the Silberbergs (7), have indicated that mammary cancer occurs in higher incidence in mice subjected to estrogen at an early age than at a later age. Similarly, the capacity of methylcholanthrene as a cancer producing agent has been well established (3). Cowdry and Suntzeff (8) found that a higher percentage of skin cancers developed in young than in older mice of the New Buffalo strain subjected to the same applications of methylcholanthrene. However, no essential difference was noted between young and old mice of the skin cancer resistant CBA strain, treated in a similar manner. Although strain characteristics may have been responsible for the failure of the CBA mice to respond in the same way as mice of the New Buffalo strain, it is noteworthy that in neither strain was there demonstrated a greater susceptibility of old than of young animals. Li and Gardner (9) noted in mice no essential difference in the susceptibility of old and young ovaries to tumorigenesis after intrasplenic transplantation. Kaplan (10) has shown in mice a decreasing susceptibility with advancing age to the leukemogenic action of x-rays.

As for the observations on humans, wherever a direct or contributing external stimulus to cancer formation can be determined, nearly all evidence points to the importance of the time at which the stimulus was applied and to the duration of the stimulus rather than the age of the person. For example Kennaway and Kennaway (11) in a review of the incidence

and incubation time of human cancers related to stimuli have pointed out that the incidence of cancer of the lung in miners of the Schneeberg, Joachimstal and Griesheim mines was far higher than in the general populations, but that the age at death was not appreciably different. In the same manner, the incidence of scrotal cancer in chimney sweeps and mule skinners does not differ greatly in age from the general population, but mainly in degree. Earlier observations of cancer occurring at a younger age in chimney sweeps are perhaps accounted for by the employment of children in this occupation before the enactment of child labor laws. In contrast, these authors cite the relatively early age incidence of cancer associated with familial polyposis of the intestine and xeroderma pigmentosum. Genetic factors would thus appear largely to govern the time of appearance of certain types of cancer and their potential incidence, whereas environmental factors seem to govern the actual incidence. The latent period for cancer growth, assuming H and S to be of sufficient magnitude, would thus determine the time at which cancer developed, and the usual age incidence of cancer is a reflection of the incubation or latent period rather than of any inherent disposition of aged tissues to cancerous change. In the case of bone tumors, which in young persons appear in many instances to follow trauma, a strong genetic factor must be assumed to be present if the trauma is to be at all related to the tumor, because some degree of trauma is an almost inevitable consequence of youthful activity in general. The high incidence of osteogenic sarcoma in Paget's disease of bone, a chronic disturbance of bone formation in older age, would attest to the need of a considerable stimulus in the bones of older persons before neoplastic growth could be established. The frequency of fractures of the femur in elderly persons is in contrast to the extreme rarity of osteogenic sarcoma at the site of fracture. Both Woglom (12) and Hueper (13), after extensive investigations, have expressed the view that advanced *age is* unimportant or fortuitous in the development of cancer. Similarly, Seelig and Cooper (14) in a review of the literature of tar cancer, presented no evidence of a relationship to ageing processes.

What Is Known About the Causation of Cancer Which Would Relate the Disease to Old Age?

Knowledge as to the causation of cancer has been gained largely by careful analyses of genetically controlled experiments or by observations of specific types of cancer, and the voluminous literature on the subject cannot be reviewed here. Much of it is summarized in Hueper's "Occupational Tumors and Allied Diseases" (13). If one accepts the equation, $H \times S = C$, proposed by Loeb (4), the majority of experimental evidence

leads to two conclusions: The earlier the stimulus is applied, the more effective it is; and the effectiveness of the stimulus depends not only on its intensity but also on its duration. Perhaps in all instances, the stimulus should be regarded as having multiple components or factors. Some of these may need to act over a period of time preceding the action of an inciting factor. The experiments of Mottram (15), in which a single stimulus (application of benzpyrene) to the skin was effective in producing cancer only when the tissue was sensitized by previous application of croton oil or croton resin, illustrate this principle. Ageing as such is thus not directly concerned with the genesis of cancer. It is probable that such a sequence of events must be taken into consideration in evaluating the reports of human cancer apparently originating from a single stimulus, usually a trauma. Nevertheless, in such cases, some information may be obtained as to the time required for cancer development in relation to age of the host. In the series of skin cancers reported by Leighton and Schmidtke (16), which followed trauma, it is noteworthy that the trauma occurred in most instances three years or less before recognition of the cancer, and that many of the cancers developed in persons younger than is usual for lesions of the types described. It was not evident in the series that the age of the host was a considerable factor in cancer development, either with regard to the length of the latent period following the inciting stimulus or to the age at which the stimulus occurred.

Of the cancers arising in secondary or accessory sex organs, which appear to depend more or less upon the endocrine secretions of the gonads for development, there is such variation in their average age incidences as to discredit the thesis that ageing as such is the most important factor in their production. Cancer of the cervix has been found in most surveys to have its greatest incidence at a lower age than that of common types of cancer arising in tissues presumably not under hormonal influences. In contrast, cancer of the prostate occurs largely in persons of advanced age. The stimulating factors necessary for the development of prostatic carcinoma must either appear late in life or require a long period of activity before cancer is produced. On the other hand, evidence that prostatic cancer may grow slowly and therefore not present clinical signs generally until at an advanced age is furnished by the studies of Moore (17) in which he found that latent carcinomas were present in the prostates of 20 per cent of men beyond the age of 50. The possibility that there may be more than one fundamental type of prostatic cancer, each with its characteristic age incidence, causes and growth rate, cannot be excluded; but the observed continued increase in clinical incidence with advancing age (3) indicates that all may eventually follow the same pattern if given enough time.

Experiments already cited, where established causative agents have not produced cancer more readily in old than in young animals, may also be offered as evidence that our knowledge of the causes of cancer has not been able to relate the disease directly to old age.

Is the Incidence of Cancer a Direct and Continuous Function of Age?

The incidence of cancer in a species is of course a summation of the incidences of the various recognized types of cancer, and the reservation should be made that even when grouped according to organ and microscopic appearance, each category may not be entirely homogeneous within itself. A classification based on etiology is not possible in the present state of knowledge about the causes of cancer. As will be exemplified below, most types of cancer, in man or experimental animals, which occur with sufficient frequency to merit tabular or statistical analysis, have a rather characteristic age incidence. The incidence of total human cancer appears to be more nearly a continuous function of advancing age than do individual types, largely because the different patterns of incidence of the various types are thus superimposed.

We have recently analyzed the incidence of cancer in the autopsy records of the St. Louis Municipal Hospitals during the fifteen year period from July, 1935, to July, 1950 (18). A total of 12,443 autopsies were performed on white patients ranging from prematurity to a stated age of 105 years. Of these 2,322 bore cancers, or 18.7 per cent. That the sample was fairly representative of the community is attested by close agreement of the age distribution with that of the total reported mortality in St. Louis during the period. Further evidence for the representative character of these data is that the peak incidences of the various types of cancer conformed well to observations of others, with the exception of skin cancer, which could not be determined accurately at autopsy. In this series an analysis of the ten most common forms of cancer has shown that each type had a characteristic age distribution, and, except for prostatic cancer, the peak incidences were between the fourth and seventh decades. In order to answer more exactly the question as to the relation between incidence and age, the data were calculated in the manner of a table of expectancy for each type of tumor. The number of persons alive in the series at the end of each decade was divided into the number of tumors which occurred in those individuals in subsequent decades, thus giving in a crude form the expectancy of tumor development with advancing age into senility. The expectancy of the six most common types of cancer is shown graphically in Figure 1. In each instance, except for cancer of the prostate, the expectancy decreased with advancing age in the older age groups.

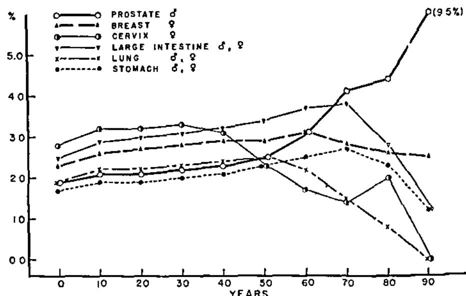


FIG. 1. Expectancy of six common types of cancer, based on autopsy records of St. Louis Municipal Hospitals, 1935–1950. Expectancies of cancer of large intestine, stomach and lung are calculated for males and females of the autopsy series, those of cervix and breast for females only, and of prostate for males only.

Most observations of spontaneous cancers of animals have indicated characteristic age incidences for each type of cancer. Murray and Little (19) calculated the frequency of mammary cancer in mice of the dba and hybrid strains and showed that the expectancy of cancer decreased in advanced age. It is noteworthy that mice of a high leukemia strain (AK) developed leukemia within rather distinct age limits, with the peak of incidence in the eighth month of life (20). In another experiment using the same strain, leukemia was not found in control mice less than 5 months old, and no instance was observed in control animals surviving beyond the age of 14 months (21). Similarly, the incidence of pulmonary lymphosarcoma of rats (Yale strain) was found to decrease slightly in advanced age (22). This tendency was not noted in the case of adenomas of the pituitary (23), which were rarely fatal of themselves.

These observations indicate that the incidence of specific types of cancer is not a continuous function of age and that the factors of cancer development are perhaps independent of ageing. Where the incidence continues to rise with advancing age, as in the case of prostatic cancer, the implication is either that some of the tumors of this type may grow extremely slowly and thus not be fatal within the natural life span, or that factors of stimulation may act over a relatively long period. Such tumors would seem to be exceptions to the general pattern of incidence and do not entirely

discredit the possibility that an individual, properly constituted genetically, may outlive the "cancer age".

Is the Behavior of Cancer Modified by the Age of the Host?

The well established observations that the forms of cancer which occur in young people are disproportionately embryonic or poorly differentiated and that the course of such types of cancer is usually rapid, do not constitute an answer to the question. In view of the examples of cancer in young persons with familial diseases such as intestinal polyposis and xeroderma pigmentosum, the sporadic cases of Wilm's tumor, leukemia, osteogenic sarcoma, neuroblastoma and brain tumor suggest in the young hosts the existence of a high constitutional or genetic disposition to malignant growth, either general or tissue specific. In such instances the genetic makeup would seem largely to govern the potential incidence and the time of appearance of the tumors. The relatively low frequency of malignant tumors of childhood in the general population, as contrasted to that of later life, would further suggest that since such tumors are almost uniformly fatal before maturity, the opportunity for transmission or intensification of any hereditary components is kept at a minimum. It seems probable that the clinical impressions of the course of such tumors of childhood are carried over into an appraisal of the behavior of common types of cancer in young and old.

Properly, the answer should be sought in a comparison of the morphology and behavior of the same types of cancer at different ages. Lees and Park (24), in a study of cancer at different ages found no significant differences in histological appearance relative to age except doubtfully in carcinoma of the lung. These authors also reviewed the evidence from the literature as to the relation of age to duration of untreated cancer and to curability rate. The reports of the various authors cited, often contradictory, did not support the thesis that cancer is more malignant clinically in young than in old patients. Furthermore, Kirschbaum and Preuss (25) noted that, except for stem cell leukemia, acute leukemias were not more common at autopsy in young than in older persons. It is difficult if not impossible to obtain accurate information as to the duration of internal cancers because the onset of symptoms depends to so great an extent upon the exact localization of the growth and upon the degree to which the patient may react to pain or discomfort. A brief attempt to correlate the duration of recorded symptoms with age at death of cases of lung cancer in the autopsy series of the St. Louis Municipal Hospitals indicated such variations at all ages as to discourage further analysis. A tabulation of the degree of differentiation of lung cancers of the same series in relation to age showed a slightly greater number of undifferentiated than differentiated cancers

in persons under 60 years of age and a few more differentiated than undifferentiated cases in persons past 60 years (26). However, the differences were not great and were not statistically significant. In evaluating reported differences in morphology of cancer with age, the possibility should be considered that two or more distinct types of neoplasm, each with its characteristic age incidence and perhaps causative factors, may have been confused and that the differences observed may in reality be only the distinguishing of one type from another.

Observations of so-called spontaneous tumors of animals have disclosed no conspicuous differences in behavior or morphology relative to the age of the hosts, although we know of no studies which have been directed primarily to this problem. No age differences were noted in the morphology of pulmonary lymphosarcomas or hypophyseal adenomas in rats (22, 23); and within high tumor strains of mice, no differences relative to age have been reported in the microscopic appearance of pulmonary adenomas, mammary carcinomas or leukemias, although these tumors have been described in detail (27). The relation of age to the rate of growth of transplanted cancers has received some attention. Nettleship (28) was not able to show that transplanted lymphomas grew more rapidly in young than in old mice. Additional experiments and observations are needed, but from the evidence available it cannot be stated that the behavior or morphology of cancer is significantly modified by the age of the host.

Summary

In this chapter we have attempted to answer several questions arising from the postulated relations between ageing and cancer. The processes of ageing as such do not favor cancer formation, except perhaps indirectly by prolonging periods of cellular activity following injury or through a lessened ability of the older tissues to restrain the cyclic growth of cells. Cancer has not been induced more readily in old than in young experimental animals. Known factors in the causation of cancer relate it to ageing chiefly because a long period of stimulation or latent period following stimulation appears to be required for the development of cancer. Genetic factors determine not only the potential incidence, but largely the age at which the cancer may appear. Genetic factors thus appear to determine the latent period to known or supposed stimuli.

The incidence of cancer, or of specific types of cancer, is not a continuous function of advancing age. The decreasing incidence or expectancy of certain forms of cancer in advanced age is probably more a reflection of genetic makeup than indicative of the absence of stimuli. The increasing incidence of prostatic cancer in advanced age is perhaps indicative of a slow rate of

growth. There is no reliable evidence that the age of the host modifies the appearance or behavior of cancer.

In general, the pattern for cancer is set long before the appearance of the disease. There is evidence, cited by Woglom (12), that when the preliminary changes which are to culminate in malignant growth have taken place, a tumor will follow even though the stimulus is withdrawn. The experiments of McCay, Sperling and Barnes (29), Tannenbaum (30) and others have shown that caloric restriction of the diet will decrease the incidence and postpone the time of appearance of many spontaneous tumors, especially if instituted in early life. McCay and associates (31) found that underfeeding at a later age was not effective. Moreover, the experiments of Furth (32), in which life was prolonged and leukemia largely prevented in high leukemia strain mice by thymectomy at an early age, point also to the importance of the early period of life in the genesis of cancer.

Except in the field of nutrition, where the relations are so complex as to defy more than partial analysis, the problem of reduction of cancer incidence must be defined for each type of cancer. Progress has been made especially in the case of external cancers and those where a relation to environment could be established. The prospects for the control of the genetic basis of human cancer are necessarily poor but the demonstration of extrachromosomal influences in mice, such as the milk factor of Bittner (33) and the effects of litter seriation on the behavior of induced tumors noted by Strong (34), are hopeful indications that many of the factors regarded as genetic may yet be resolved into components which can in some measure be controlled.

However, there is every prospect that cancer as a clinical problem will increase in importance, because cancer, although not a direct effect of ageing, does reach its greatest incidence in middle or advanced age, and an increasing percentage of the population is attaining this "cancer age".

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Section III

CHAPTERS 37 TO 40

SOCIAL AND ECONOMIC PROBLEMS OF AGEING

37

TRENDS IN THE AGEING POPULATION

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In April, 1950, the Seventeenth Decennial Census of the United States reported that the average person in this country was over 30 years of age When the First Decennial Census of the United States was taken in 1790, the average person in this country was about 16 years of age In a dramatic way, these figures summarize the ageing of the population in the United States, a process which has been under way for at least as long as we have census records (see table 1).

The ageing of the population is not a phenomenon unique to this country. It is a population trend discernible in all the nations which share Western Civilization. The increasing average age of the people of Western Countries is but one of a number of the demographic consequences of that series of technological, economic, and social changes which are epitomized in the expression "The Industrial Revolution". The attainment of relative old age by a large proportion of the human population is a modern invention. It is just as much an innovation in the history of man as are certain technological developments, the electric light or the automobile, for example. "Problems of ageing", as they relate to large segments of a population may be considered as relatively new problems—as new as many of the other problems of an industrial society.

The populations of those European countries which experienced industrialization before the United States showed signs of ageing earlier and have progressed further in the ageing process.

In 1850 4.1 per cent of the total population of the United States were 60 years of age and older. Fifty years later, in 1900, this percentage had increased to 6.4 per cent, and by 1947 to about 11.5 per cent. In France 10 per cent of the population was 60 years old and over in 1850, and 16 per

cent in 1947. In England and Sweden over 7 per cent of the population were in these age categories in 1850, and 15 per cent in 1947 (see table 2).

TABLE 1

Average age (median) of population of the United States by sex and by color, 1790–1950

Year	Total	Sex and color			
		Male	Female	White	Non-white
1790	—	—	—	15.9*	—
1810	—	—	—	16.0	—
1830	17.2	17.1	17.3	17.2	16.9
1850	18.9	19.2	18.6	19.2	17.4
1870	20.2	20.2	20.1	20.4	18.5
1890	22 0	22.3	21.6	22.5	18.4
1910	24.1	24.6	23.5	24.5	21.1
1930	26.5	26.7	26.2	26.9	23.5
1950	30.1	29.9	30.4	—	25.5

* White male only.

Source: U. S Bureau of the Census. Historical Statistics of the United States, 1789–1945 (Washington, D. C , 1949), Series B72–80 p. 27.

Data for 1950 from U. S. Bureau of the Census. General Characteristics of the Population of the United States., April 1, 1950. 1950 Census of Population, Preliminary Reports, Series PC-7, No. 1 (Washington, D. C., Feb. 25, 1951).

TABLE 2

*Percentage of persons 60 years of age and over in the United States and in selected countries, 1850, 1900, and 1947**

Country	About 1850	About 1900	End of 1947
United States†	4.1	6.4	11.5
England	7.2	7.5	15.2
France	10.1	12.4	16.0
Germany	7.0	7.8	13.8
Sweden	7.8	11.9	15.3
The Netherlands	7.7	9.2	11.6
Denmark	8.2	9.9	13.1
Norway	8.8	10.9	13.7

* Data for countries other than United States adapted from Alfred Sauvy: Social and Economic Consequences of the Ageing of Western European Populations. Population Studies, II (June, 1948) p. 115

† Estimated as of July 1, 1947—U. S. Bureau of the Census: Population Estimates. Current Population Reports, Series P25-No. 39 (May 15, 1950, Washington, D. C.).

The proportion of older persons in a population can be used to differentiate the more "advanced" and industrialized regions of the world from the relatively "backward" ones. Approximately 7 per cent of the

world population was 60 years or over in 1947. In the industrialized areas of the world, including the United States, Canada, Northwest and Central Europe, Southern Europe, and Oceania, between 10 and 14 per cent of the total population were 60 years of age and over. In areas under the initial impact of industrialization—Eastern Europe, Japan, and the Near East—persons 60 years old and over constituted 6 to 8 per cent of the total

TABLE 3

Estimated percentages of population in three major age groups in various regions of the world, around 1947

Region	Estimated percentage of population		
	Under 15	15–59 years	60 years and over
World Total.	36	57	7
Africa	40	55	5
America			
U. S. A. and Canada	25	64	11
Latin America	40	55	5
Asia			
Near East	40	54	6
South Central Asia	40	56	4
Japan	37	55	8
Remaining Far East	40	55	5
Europe			
Northwest Central Europe	24	62	14
Southern Europe	30	59	11
Eastern Europe* .	34	59	7
Oceania .	28	62	10

* Including the Asiatic part of the U.S.S.R. Source: United Nations, Department of Social Affairs World Population Trends: 1920–1947 (Dec. 1949) p. 15

population. In those areas which are still largely pre-industrial—South-central Asia, Africa, and the Far East excluding Japan—the proportion of the population 60 years of age and over was only 4 to 5 per cent[1] (see table 3).

The increase in the number and proportion of older persons in the United

[illegible]

proportion of older people.

States may, then, be considered but one manifestation of the world wide demographic revolution which has accompanied the Industrial Revolution. The growing number of aged is but one of a series of related population changes. This will be even more apparent from a closer examination of the changing age structure of the population of the United States.

The Changing Age Structure of the United States

On April 1, 1950, the population of the United States totalled 150½ million. Persons under 20 numbered 51½ million, and persons 60 and over, 18 million. During the 100 years between 1850 and 1950, while the total population increased six-fold and the number of younger persons only four-fold, the number of older persons increased eighteen-fold (see table 4).

As a result of these changes there has been a considerable shift in the ratio of persons in the potentially dependent ages, that is, under 20 years and 60 years of age and over, to persons in the productive ages, that is persons between the ages of 20 and 59. A century ago, for every 100 individuals in the productive age group, there were 130 persons in the potentially dependent group, of whom 121 were under 20 years of age and only 9 were 60 years of age or over (1). By 1950, for every 100 individuals of productive age, there were only 86 persons in the potentially dependent age group. Sixty-four of these were under 20 years of age, while 22 were 60 years of age or over. The ratio of all persons in the dependent ages to all persons in the productive ages decreased by 34 per cent in this century. The ratio of persons under 20 years of age to the productive group decreased by 47 per cent, however, while the ratio of persons 60 years and over to persons of productive age increased by more than 140 per cent (see table 5).

The changes in the population structure of the United States are increasing the numbers and proportion of older, potentially dependent persons and this trend will undoubtedly continue for some time to come.

Factors in Ageing

Changes in the number and composition of the population are effected through the interaction of three factors: fertility, mortality, and immigration. The interrelationships of births, deaths, and population movements have been profoundly affected by our changing way of life. Industrialization and its related technological, economic and cultural changes generally resulted in a decline in mortality and fertility and set in motion waves of immigration of peoples within and across national boundaries.

Each change in the pattern of birth or death rates or in the volume of immigration is reflected in the age structure of a population. In both the short and long run a declining birth rate decreases the proportion of young

TABLE 4

Age distribution of population of the United States, 1870–1950

(Thousands)

Year	Total*	Under 5	5-14	15-24	25-44	45-64	65 plus
		Number					
1870	36,553	5,515	7,601	7,789	9,892	4,602	1,154
1890	62,460	7,635	14,608	12,754	16,858	8,188	1,417
1910	91,894	10,631	18,868	18,121	26,810	13,424	3,950
1930	122,679	11,444	24,612	22,422	36,153	21,414	6,634
1950	150,697	16,321	24,602	22,059	44,495	30,444	12,322
		Percentage					
1870	100	15.1	20.8	21.3	27.1	12.6	3.2
1890	100	12.2	23.4	20.4	27.0	13.1	3.9
1910	100	11.6	20.6	19.7	29.2	14.6	4.3
1930	100	9.3	20.1	18.3	29.5	17.5	5.4
1950	100	10.8	16.3	14.6	29.8	20.2	8.2

* Excludes "age unknown" except for 1950

Source: U S Bureau of the Census Historical Statistics of the United States, 1789–1945 (Washington, D C, 1949) Series B81–144, p 27

Data for 1950 from U S Bureau of the Census General Characteristics of the Population of the United States, April 1, 1950 1950 Census of Population, Preliminary Reports, Series PC-7, No 1 (Washington, D C, Feb 25, 1951)

TABLE 5

Number of persons of dependent ages (under 20 years and 60 years and older) per 100 persons in productive ages (20 to 59 years) in the United States, 1850–1950

Year	Persons in the dependent age groups per 100 persons in the productive age group		
	Total	Under 20	60 years and older
1850	130	121	9
1870	121	110	11
1890	110	97	13
1910	96	82	14
1930	90	74	16
1950	86	64	22

Source Adapted from Philip M. Hauser, Some Implications for Capital Investment of the Population Changes Revealed in the 1940 Census Paper given at Thirty-fifth Annual Meeting, American Life Convention, Chicago, p. 15, Oct. 7 to 10, 1940.

Data for 1950 from U. S. Bureau of the Census. General Characteristics of the Population of the United States; April 1, 1950. 1950 Census of Population, Preliminary Reports, Series PC-7, No. 1 (Washington, D C., Feb. 25, 1951).

people and results in an increased proportion of older people. A declining death rate, in the short run, also increases the proportion of younger persons because mortality gains are greatest for infants and younger persons. In the long run, however, decreasing mortality increases the number and proportion of older persons. Immigration into a country in any quantity usually tends to increase the proportion of younger persons since immigrants are usually young adults. The opposite effect occurs in the population structure of a country with prolonged emigration.

In the United States declining fertility and mortality have operated historically to produce an ageing population. Until the passage of restrictive immigration laws in the 1920's the tendency toward ageing was retarded by the influx of large numbers of immigrants. With the decline in immigration and the changes in birth and death rates which have occurred since the 1920's the population of the United States has aged more rapidly than ever before.

Death rates in the United States have been declining for at least as long as any records are available. The data for the period before 1900 are fragmentary. In 1850, however, expectation of life at birth, a summary measure of the death rate at all ages, was 38.3 years for white males in Massachusetts. By 1900, Massachusetts male expectation of life at birth had increased to 44.3 years and by 1940, to 63.3 years (2). For the original registration states in the United States in 1900, the life expectation for white males was 48.2 years. By 1948, life expectancy for white males in the Continental United States had increased to 65.5 years.

From these data it would seem that between 1850 and the present, expectation of life at birth has increased by about 27 years for white males. The corresponding increase for white women has been about 30 years—an increase of about 70 per cent in average longevity.

The most phenomenal declines in mortality have occurred in infant mortality and through the conquering of infectious diseases. As a result, expectation of life has not increased uniformly at all ages of the population. In the first half of this century, while the expectation of life at birth for white males increased by over 17 years, expectation of life for those at age 20 increased by less than 7 years, at age 40 by 3 years, and for those who had reached 65, by only one year (3).

The relatively small gains since 1900 in the expectation of life of those at the higher ages focus attention on the next frontier in the conquest of disease—chronic and degenerative conditions. One third of all deaths in 1900 were attributable to pneumonia, influenza, and tuberculosis, diseases of the younger and middle years. By 1948 these three infectious diseases accounted for less than 7 per cent of all deaths. The leading causes of death in 1948 were diseases of older persons—heart diseases accounting for almost

one-third of all deaths, cancer accounting for one-seventh of all deaths, and cerebral hemorrhage and nephritis (3).

Like the death rate, the birth rate of the United States also has been declining for at least as long as records are available. It has been estimated by Thompson and Whelpton that in 1800 the birth rate was at a level of 55 per 1000 (4). By 1940, the birth rate had declined to 17.9 per 1000, roughly one-third of its 1800 level. Since 1940, the United States has experienced a sharp cyclical upswing in the birth rate (5). This cannot be interpreted, however, as a reversal in the long-run decline.

Immigration has made an important contribution to the total population of the United States and to its age structure. Between 1820 and 1950 almost 40 million immigrants entered the United States. The peak in immigration was reached during the decade between 1900 and 1910 when almost 9 million foreign-born persons entered this country. Since that time the volume of immigration has fallen off sharply, and, indeed, stopped almost completely after the passage of the quota immigration laws.

Between 1930 and 1940 emigrants from this country actually exceeded the number of newcomers by about 50,000 people. Between 1940 and 1950, even with special provisions for refugees and displaced persons, net immigration into the United States barely reached one million.

Despite the belief of many persons, including some in the medical profession, that the decrease in the death rate has been the most important factor in the ageing of the population in the United States, this has not actually been the case up to the present time. Warren S. Thompson has indicated that the factors in the ageing of the population, in order of importance are: declines in fertility, declines in mortality, and declines in immigration (6). Dr. Valaoras has documented this conclusion in a recent paper (7). One reason that declining fertility has been a more important factor in population ageing than declining mortality is the fact that most of the mortality gains achieved to the present have been at the younger ages. In the coming decades, however, it is expected that declining mortality will increase in its relative importance as a factor responsible for the ageing of our people.

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1940 than occurred in the 30 years between 1890 and 1920. The median age of the population increased by only 3.3 years between 1890 and 1920, and by 3.7 years from 25.3 to 29.0 between 1920 and 1940. The great increase in the birth rate since 1940 has somewhat retarded the ageing process.

Up to this point we have discussed persons 60 years and older as constituting the aged. This has been an arbitrary definition useful for inter-

national comparison and for reconstructing the historical trends in the United States in the past century. Since in recent censuses more detailed information is available for persons 65 years of age and over, the remaining materials will focus largely on persons in this age category.

Characteristics of Older Persons

Older persons in the United States differ considerably in general population characteristics from the total population. The 1940 Census of population provides the most recent data for a detailed analysis of these differences, although in some instances, later data are available from sampling studies.

In 1940, there were somewhat more than 9 million persons, 65 years of age and over in the United States, making up almost 7 per cent of the total population. The ratio of men to women in this older group differed from the sex ratio of the general population. Although in the total population males were in the majority (50.2 per cent), women outnumbered men among older people, constituting 51 per cent of the older group. This may be expressed in another way by saying that in the total population there were 100.7 men for each 100 women, while in the older group there were 95.5 men for each 100 women. This excess of women compared to men becomes increasingly marked in the ages above 65. At age 75 and over, for example, there were only 88 men for each 100 women (8). These differences in the sex composition of our older population, which become greater with age, result from the lower mortality rates for women. A white female born in 1948 had a life expectancy of 71.0 years, while a white male, for the same year, had a life expectancy of only 65.5 years (9). Interestingly enough, the differences in life expectancy between men and women has been increasing steadily.

The older age group also differs significantly from the total population in their color and nativity. Compared to the total population, older people include a greater proportion of foreign-born persons, and a lesser proportion of non-whites. Roughly 1 of every 5 older persons is foreign-born, compared with 1 of every 10 persons in the total population. This sharp difference results from the restriction in immigration which, if continued, will virtually eliminate the foreign-born as a significant proportion of our population. While over 10 per cent of the population of the United States have been classified as non-whites, only 7 per cent of older persons are in this category (10). Here we see the result of the differential death rates for whites and non-whites, with the higher death rates of the latter group leaving a smaller number of persons in the older age brackets.

The marital status and family living arrangements of older people also differ from the total population. In 1949, according to a sample survey of

the Bureau of the Census, well over half (54 per cent) of older women were widowed. Only 12 per cent of all females 14 years of age and over were widowed. Approximately one-third (37 per cent) of the older women were married, as compared with two-thirds (66 per cent) of all women 14 years of age and older. Only 8 per cent of the older women were single, compared with 20 per cent of the total female population

Because of the differential death rates by sex, a lesser proportion of older men than of older women were widowed. Nevertheless, almost one-fourth (24 per cent) of men 65 years of age and over were widowed, as contrasted with only 4 per cent of all men 14 years of age and over Approximately the same proportions of older men and of men 14 years of age and over were married, 66 per cent as compared with 68 per cent Only 8 per cent of the older men, compared with 26 per cent of all men 14 years of age and over, were single. In the total population 65 years of age and over, 39.8 per cent were widowed, 8.2 per cent were single, and 50 7 per cent were married persons. Thus, almost half of all older people were unmarried persons, a factor which plays an important part in the living arrangements of this age group (11).

Most of our older people live in private households, as distinct from what the Census calls quasi-households, which include institutions, rooming houses, transient hotels and the like. A significantly large proportion of old people, however, do not live with relatives, although they are members of private households. Of the total population 65 years of age and over in 1949 slightly more than three-fourths (78.4 per cent) lived in private households with related persons. About one-sixth (17.3 per cent) lived in private households with persons to whom they are not related, and about 1 in 23 (4.3 per cent) lived in quasi-households. Thus, over one-fifth of our older people (21.6 per cent) are spending their later years in living arrangements apart from their families or relatives.

The living arrangements of older women are quite different from those of older men. Women live longer than men, and consequently more of them are [illegible] three-fourths of the won [illegible] pared with over four [illegible] rsons in private households. A large proportion of women, over one-fifth (21.5 per cent) as contrasted with one-eighth of the men (12.5 per cent), live in private households with persons who are not related to them. On the other hand, only 1 in 36 of the older women (2.8 per cent) compared with 1 in 17 of the older men (6.0 per cent) live in quasi-households. As a result, one-fourth of all older women, as compared with one-fifth of older men, find it necessary to accommodate themselves to non-family living arrangements in their later years (12).

Finally, an examination of the education background of the older population is important because of its implications for programs dealing with older people. As we know, in recent decades increasing proportions of the population have had the opportunity to obtain higher forms of education than that represented by the older exposure to the "three R's". It is not surprising therefore, that there is a high inverse correlation between age and years of formal education. Older persons are predominantly a group with only grade school education. In 1940, persons 65 years of age and over had on the average (median) 7.7 years of schooling, or slightly less than a completed elementary school education. In contrast, all persons, 25 years of age and over, had completed 9 years of schooling on the average, or 1 year of high school training. The group 25 to 29 years of age had completed on the average 12 years of schooling or the equivalent of 4 years of high school. Almost three-fourths of all older persons (72.4 per cent) had 8 years of school or less, and one-fifth of all older persons reported that they had completed less than 5 years of school. Less than half (49.5 per cent) of all persons 25 years of age and over reported 8 grades of school, and only one in ten (10.8) had less than five grades of school. Only one-tenth (9.8 per cent) of the older people had completed high school, and only one in thirty (3.3 per cent) had completed college. In the population 25 years of age and over, over one-fifth (20.5 per cent) had completed high school, and one in nineteen (5.4 per cent) had completed college (13).

Geographical Distribution

The older population is not distributed in a uniform manner throughout the United States. Differential fertility, mortality and migration between states have produced discernible differences in the geographical distribution of our older citizens. On a broad regional basis in 1948, both the largest number of persons 65 years of age and over and the highest proportion of such persons were to be found in the North Central states as these are defined by the Census. These twelve states[2] had 3,633,000 persons in the older age group who constituted 8.4 per cent of their total population. In the North Eastern states and in the Western states exactly the same proportion, 7.9 per cent of the total population, was 65 years of age and over, although the former states included the larger number of older persons, 3,065,000 compared to 1,509,000. The South with 2,731,000 persons in the older age group had the smallest proportion of older people in its population—6.1 per cent.

Among the individual states, the proportion of older persons, estimated at 7.5 per cent for the United States as a whole, varied from about 5 per

[2] Ohio, Indiana, Illinois, Michigan, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, and Kansas.

cent in New Mexico to about 10 per cent in New Hampshire. Older people were found in larger proportions (between 9 and 10 per cent) in the New England states of Maine, Vermont and New Hampshire and in some of the Corn Belt states, Iowa, Kansas and Missouri. The states with the smallest proportion of older persons (ranging from 4 to 6 per cent) were concentrated in the South, South Carolina, North Carolina, Alabama, Louisiana, Mississippi and Georgia, and in the Mountain States, New Mexico, Arizona and Utah. Despite the prevalent belief that Florida and California are the *two states with the highest proportion of older people*, only 7.3 per cent of the population of Florida and 8.1 per cent of the population of California were 65 years of age and over in 1948 (14).

The proportion of older persons in the total population also varied by city size and by whether the area is farm or non-farm rural district. For urban United States as a whole in 1940, 6.8 per cent of the population was 65 years of age and over. There was an inverse correlation, however, between the size of the city and its percentage of older people. Those 65 years of age and over constituted only 6.5 per cent of the total population in large cities of 100,000 or more. In cities of 10,000 to 100,000 they were 7.0 per cent of the population and in places from 2,500 to 10,000 population, 7.6 per cent.

The proportion of older persons in rural farm areas approximated their proportion in the larger cities (6.6 per cent) (15). The low proportion of oldsters on farms is a result of the relatively high birth rate which prevails in these areas. In large cities, on the other hand, the influx of many young people from the surrounding country tends to lower the proportion of older persons.

In rural non-farm areas the proportion of older people is 7.3 per cent. Rural non-farm areas as defined in the 1940 Census, however, include a heterogeneous population of suburban dwellers in large metropolitan centers as well as village residents and non-farm dwellers located in the open country. A more meaningful analysis of the older population in rural non-farm areas must, therefore, await a more precise definition of this type of area which will be forthcoming in the 1950 Census.

In summary, on a geographical basis persons in the older years are most greatly represented in the population in the North Central States and in certain New England states and least represented in the South and in parts of the West. In general, older persons are also overrepresented in our medium-size and smaller cities. An analysis of the geographical distribution of older citizens discloses that the differences in their distribution result largely from the interaction of the birth rate and selective migration. The areas with relatively low proportions of persons 65 years of age and over tend to be areas of high birth rates, such as the South, and of high immi-

gration, that is, the large cities. The areas with relatively high proportions of older people tend to be the areas with low birth rates or areas of high outmigration. Despite the general impression that large numbers of older persons flock to Florida and California, the proportion of older people in these states is not extremely high. The migration of younger persons, rather than the relatively small movement of older people, is the major factor in accounting for the proportions of older people in the various regions of the United States.

Participation in the Labor Force

For the vast majority of our older people, as well as for our population at large, employment is the predominant medium through which self-support is achieved and dependency avoided. In our society, especially for men, employment is also a major ingredient of satisfactory social and psychological adjustment. For these reasons the relation of the older population to the labor market is of special interest.

Within the last 60 years, despite the sharp decline in the labor force participation rates of both younger and older persons, the median age of workers has risen considerably. In 1890, the median age of male workers was 33.3 years, that of female workers, 24.3 years. In 1950, the median age of male workers was 38.0, and of female workers, 36.4 years. Reflecting our ageing population, in 1950, over one-third (34.7 per cent) of the labor force was 45 years of age and over. In 1890 about one-fourth (24.5 per cent) of the labor force was in this age group (see table 6).

The proportion of all men 45 years or older in the labor force declined from about 87 per cent in 1890 to 79 per cent in 1950. In this 60-year period, the proportion of men in the 45 to 54 year age group in the labor force remained practically unchanged, but the labor force participation rates of men 55 years of age and over, decreased appreciably. For men 55 years to 64 years of age, these rates dropped from 88 to 85 per cent, and for men 65 years of age and over, from 68 to 45 per cent. As may be seen, the major factors in accounting for the lower proportion of men over 45 in the labor force has been the decline in employment for men in the older years.

Labor force participation rates for women in the ages above 45 are relatively low. The trend toward increased employment among women, however, has been reflected in a steady rise in labor force participation rates for both older and younger women. Thus, while only 11 per cent of the women over 45 years of age were in the labor force in 1890, 26.2 per cent were employed in 1950 (see table 7).

The decreasing participation in the labor force of older male workers mentioned above is one of the most important aspects of our ageing popu-

lation, since it involves the whole question of the economic status and dependency of older persons. Despite the fact that the total number of persons 65 years of age and over has quadrupled in the period since 1900,

TABLE 6

Percentage distribution of the labor force by age groups 1890–1950

Age group	Year					
	1890	1900	1920	1930	1940	1950
Total	100 0	100 0	100 0	100 0	100 0	100 0
14-24	30.9	30.9	25 9	23 9	22 3	19 7
25–44	44 6	44 7	46 3	46 7	46 6	45 6
45-64	20 2	20 4	23 8	25 1	27 1	29 9
65 and over	4 3	4 0	3 9	4 3	4 1	4 8

Source: Data adapted from John D. Durand, The Labor Force in the United States, 1890–1950. Social Science Research Council, New York, 1948, and U. S. Bureau of the Census, Monthly Report on the Labor Force

TABLE 7

Percentage of persons aged 45 and over in the labor force, by age and sex, 1890–1950

Age and sex	Year					
	1890	1900	1920	1930	1940*	1950
Men						
45 years and over	86 7	84 3	83 2	82 5	78 8	78 5
45-54	93 9	92 8	93 5	93 8	93 7	94 6
55–64	98 0	86 1	86 3	86 5	85 7	85 1
65 years and over	*68 2*	*63 2*	*55 6*	*54 0*	43 4	45 0
Women						
45 years and over	11 1	12 3	14 3	15 4	17 7	26 0
45-54	12.5	14 2	17 9	19 7	24.2	36.9
55–64 .	11 5	12.6	14.3	15.3	17.8	27.3
65 years and over	7.6	8.3	7.3	7.3	6.7	9 5

* Comparable to current reports of U. S. Bureau of the Census *in* Monthly Report on the Labor Force Source: adapted from John D. Durand, op. cit , and U. S. Bureau of the Census, op. cit.

while the total population of the United States has only doubled, the proportion of all workers to be found in the older age groups, 65 years of age and over, remained about the same throughout this period—4.0 in 1900 and 4.8 in 1950.

This phenomenon may be explained by the increasing retirement, volun-

tary and involuntary, of older workers from paid employment. We know relatively little about the factors underlying the withdrawals of older persons from the labor force. There is increasing evidence, however, that the withdrawal of older persons from employment is a result more of external factors than of their voluntary wish to retire. Undoubtedly many workers have personal motivations to spend their declining years in leisure, and such factors as increased savings and voluntary pension schemes, side by side with rising wages, have made voluntary retirement increasingly possible. The limited evidence available, however, indicates that most men would prefer to work rather than to retire, and it seems that *involuntary factors are relatively more significant than voluntary* ones in the withdrawal of older workers from the labor force. As declining interest rates and inflationary trends decrease the value of savings, it would seem that more and more older workers would prefer to work if employment were available to them. The introduction of compulsory retirement schemes at arbitrarily fixed ages, however, has made involuntary retirement mandatory for many. Technological changes which place less premium on skill and experience have made older workers less desirable and there is increasing evidence of discriminatory practices in the hiring and layoffs of older workers.

The economic aspects of withdrawal from the labor force, however, are more fully treated in the chapter that follows. It should be noted here, however, that the increased expectation of life, as described above, together with the decreased expectation of working life results in an increased time span between a man's retirement from the labor force and the end of his life. In 1900 a white male in the United States, age 25, could look forward to an average of 34.5 years more in the labor force and to an average future lifetime of 38.5 years. This left, on the average, a period of 4 years between retirement and death. By 1940, the life expectancy of the average white male of 25 had increased by 4 years while his work expectancy had increased by less than 1 year to 35.4 years. Thus, by 1940, the period between retirement and death for the average white male had increased 3 years to a total of 7 years. The increase in the aged population and the growing gap for individual workers between their total life, and their work life, expectancies have been basic factors underlying recent social security and private pension programs (16).

Employment opportunities and the type of employment available differ greatly for older workers as compared with the total labor force. More than 2 of every 5 workers, 65 years old and older (43 per cent) in April 1950, are self-employed as contrasted with only 1 in 8 workers under 45 years of age (13 per cent), and less than 1 in 5 workers in the total labor force (18 per cent). A little over half of the older workers (55 per cent)

are "wage or salary" workers as contrasted with almost four-fifths of the total employed (79 per cent) (17). Some of these older self-employed are persons who have gone into their own business as they have acquired experience and funds, or as they have been forced out of jobs. To a great extent, however, they represent a continuation in employment past the usual retirement ages of the self-employed person. The man who is his "own boss" can continue to work past the age when other men must retire.

The occupational distribution of older workers differs from that of the total employed—reflecting differential employment opportunity resulting from a number of factors including job requirements, compulsory retirement plans, discriminatory hiring practices and personal choice In broad summary it may be observed that older workers, that is, persons 65 years of age and more, constituted 4.7 per cent of the total employed (in April 1948). They were greatly overrepresented among farmers and farm managers (13.2 per cent), and were also overrepresented among service workers (7.7 per cent), proprietors, managers and officials—other than farm (5.9 per cent), and laborers, both farm and non-farm (5.0 and 5.3 per cent, respectively). Workers 65 years of age and more were greatly underrepresented among clerical, sales and kindred workers (2.0 per cent), and operators and kindred workers (2.3 per cent). They also appeared in less than average proportion among craftsmen, foremen and kindred workers (3.8 per cent) and professional and semi-professional workers (4.2 per cent).

The distribution of older workers by industry reveals a similar differential pattern. Constituting 4 per cent of all the employed in industry (non-agriculture), they are greatly overrepresented in the service industries (5.6 per cent) and in construction (5.1 per cent); and underrepresented in manufacturing (2 8 per cent), and in transportation, communication and public utilities (3.7 per cent) and in "all other" industries (2.9 per cent) excluding wholesale and retail trade. In the latter group they appear in about their average proportion (4.1 per cent) (18).

More specifically, older workers, whether one considers all workers over 45 or only those 65 years of age and over, are most heavily concentrated among farmers, real estate operators and anthracite miners. In April 1948, 54.5 per cent of all men classified as farmers were 45 years of age and over. The farmer group included the highest proportion of employed men 65 years of age and over, 13.2 per cent. Moreover, an analysis of the ages of workers with wage credits under Old Age and Survivors Insurance in 1947 shows that, on the average, the man employed in the real estate business is apt to be older than men in any other occupational group. More than half (50.9 per cent) of all employees in this occupation are 45 years and over and 1 in 10 (10 per cent) is 65 years and over. Anthracite mining has the next oldest age group. Roughly 2 of every 5 miners (44.5

per cent) are over 45 years of age. Among major manufacturing industries the highest proportion of workers over 45 is in the iron and steel industries, in the production of leather and leather products, in the production of lumber products, and in the manufacture of apparel (19).

The impact of unemployment differs greatly by age class. Evaluation of unemployment among older workers is made difficult by a number of factors including forced withdrawal from the labor market, partial disability, differential duration of unemployment, and part-time work. In general, however, the data indicate that except for the youngest groups of workers, those under 25 years of age who are, in the main, new entrants to the labor force, older workers tend to have the highest unemployment

TABLE 8

*Unemployment rates for males by age: 1940, 1944, 1948, and 1949**

Age and sex	1940	1944	1948	1949
14 to 19 years	32.8	3.0	8.3	11.9
20 to 24 years	18.1	2.1	6.3	9.9
25 to 34 years	10.9	0.7	2.5	4.7
35 to 44 years	11.3	0.7	2.1	3.8
45 to 54 years	12.4	0.5	2.3	3.9
55 to 64 years	14.9	0.8	2.8	4.9
65 years and over	10.0	1.1	3.0	4.9

* For 1944, 1948 and 1949, derived from weighted arithmetic means of the 12 monthly estimates. For 1940, estimated from revised 1940 Census figures and less detailed age figures for remainder of year.

Source: 1940 Census of Population, and Current Population Survey, Bureau of the Census.

rates. Both in times of high unemployment and in periods of moderate unemployment, older workers experienced higher unemployment rates than workers of intermediate age. In 1940, for example, about 15 per cent of male workers 55 to 64 years were unemployed as compared with 11 per cent for men 35 to 44 years old. In 1949 4.9 per cent of the men 55 to 64 as compared with 3.8 per cent of men 35 to 44 were unemployed (20). During periods of "full employment" such as those of the war and postwar years, older workers seem to have the same low rates of unemployment as workers in the intermediate age group. It may be expected, as the data actually reveal, that during any period of rising unemployment, older workers will experience a relatively higher unemployment rate than workers of intermediate age (see table 8).

The older worker who loses a job encounters especially great *difficulty* in finding employment. In the 1940 Census the highest proportion of workers seeking work were in the three age groups, 14 to 24, 55 to 64 and

65 years of age and over. More than 13 per cent of those in the two older age groups were seeking work and 14.5 per cent of those in the youngest group were seeking work. Analysis of the duration of unemployment indicates the greater difficulty older workers experience in finding reemployment. The percentage of those seeking work who had been unemployed for over a year rose steadily from the 25 to 34 year old age group (2.7 per cent) to those 65 years of age and over (6.6 per cent). In other words, of the 13 per cent of workers 65 years and over who were seeking work, more than half had been unemployed over a year. Almost the same figures apply to those in the age group 55 to 65 years of age.

The Prospect

Estimates of the future population 65 years old and over can be made with greater reliability than estimates of the total population. The latter requires estimation of the future course of the birth rate which is exceedingly difficult. The former requires only allowance for mortality in a population already born.

The rapidly increasing numbers of older persons at the present time and in prospect are, in the main, attributable to the increasing numbers of births in the United States in the latter part of the last century and the early part of the present century. Thus, the increase in numbers of persons 65 and over from about 3 million in 1900 to over 12¼ million in 1950 primarily reflects the increase in the annual number of births from 1835 to 1885.

As a measure of the increasing importance of the problems of ageing in the decades which lie ahead, it should be noted that it is estimated that the number of persons 65 and over will increase to between about 17 and 20 million in the United States in 1975 (21). The decrease in numbers of births in the late 1920's and early 1930's however, will produce a temporary decline in the number of older persons between 1986 and 1998—a decline of perhaps 25 per cent.

Despite such variations as reflect the cyclical variations of the birth rate, the long time trend will nevertheless, for many decades to come, result in increasing numbers and proportions of older people in the United States.

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THE OLDER WORKER IN INDUSTRY

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WHO IS AN OLDER WORKER?

Two alternative definitions

Older workers may be defined in terms of their biologic or calendar ages. The first is a physiological definition and represents a composite measure of physical capacity. It is based on a diagnostic analysis of ageing that is only as good as the quality of its interpretation (1). The second is a chronological definition which assumes a correlation between physical capacity and number of birthdays. It is an aggregate definition, based on group averages, and is applied to all members of a group without regard to individual differences. Whether an individual is classified as an older worker may depend on which definition is applied to him.

The definition employed here

Although universal adoption of the physiological definition of the "older worker" would make for a maximum utilization of the current labor force, available evidence indicates the chronological definition is more widely used. Therefore, the definition of the older worker based on the criterion of calendar age will be employed throughout this discussion. Since calendar age first affects employability at 45 for males and 35 for females, these ages will be used to define the lower limits of the older worker group.

THE ECONOMIC STATUS OF OLDER WORKERS

Older workers' needs

It is well known that consumption of goods and services varies with age. Therefore, any analysis of older workers' needs must look to the consumption patterns of the advanced age groups for its data. The Federal Security Agency has followed this procedure in preparing its "Budget for an Elderly Couple".

Briefly, this budget is for a two-person family: a husband aged 65 or more, and a wife a few years younger. Both are assumed to be retired or have only occasional employment. Included in the budget are expenditures for food, housing, clothing, medical care, and such miscellaneous items as recreation and reading, tobacco, and transportation. Wherever possible, accepted standards were used in assigning weights to the individual items. For example, the food requirements adopted were those developed by the Committee on Nutrition of the National Research Council. All items were priced from data contained in the Bureau of Labor Statistics' consumers price index (2).

Using March, 1946 prices, estimated annual expenditures for elderly couples in 13 major cities varied from $1,169 in Houston, Texas, to $1,573 in Washington, D. C. By June, 1947 the corresponding totals were $1,365 and $1,767, respectively. Although the budget has not been repriced since 1947, it is estimated that, by March, 1949, annual expenditures in the same 13 cities ranged from $1,440 to $1,830 (3).

Older workers' incomes

Age and Amount of Income. Data on income distribution in the United States are fairly complete. They indicate a pattern of individual income which rises to a peak in the 45 to 54 age range, declines slowly for the 55 to 64 age group, and more sharply thereafter. Census estimates give the following median incomes for all persons with income in 1949 (4):

Age	All persons	Female only
14 to 19	$440	$436
25 to 34	—	1,322
35 to 44	2,591	1,284
45 to 54	2,751	1,165
55 to 64	2,366	1,000
65 and over	1,016	516

For familes and unrelated individuals. Classifying the data on income distribution into these categories reveals the same relationship between income and age. The following are median incomes for specified ages (5):

Age of head	Families		Unrelated individuals	
	Income	Per cent of total	Income	Per cent of total
14 to 24	$2,364	—	$625	—
35 to 44	—	—	1,888	—
45 to 54	3,466	20.3	1,653	17.2
55 to 64	3,148	16.2	1,303	19.2
65 and over	1,883	12.0	649	27.0

For consumer spending units. The consumer spending unit is defined as "All persons in the same dwelling, and related by blood, marriage, or adoption, who pooled their incomes for their major items of expense" (6).

Comparisons of the incomes of consumer spending units classified by age of the heads of the units reveal the same age-income relationships indicated in the preceding two analyses. Spending units headed by persons aged 45 and over totaled 44 per cent of all units in 1949. They accounted for 66 per cent of the spending units with incomes under $1,000, but they comprised only 43 per cent of those with incomes of from $1,000 to $1,999, and 36 per cent of those with incomes of from $2,000 to $2,999 However, those age 45 and over headed 53 per cent of all spending units with incomes over $7,499 (7).

AGE AND MAJOR SOURCES OF INCOME. Three studies provide some indication of the sources of aged persons' incomes. The first, an inquiry made by the Federal Security Agency, was limited to individuals aged 65 and over who received income from specified sources. The 11.5 million people in this group received their incomes from the following sources:

	million
Employment	3.8
Social insurance and related programs	3.0
Old-age assistance	2.1
Total	*8 9*

The remaining 2.6 million either received their incomes from other sources or had no incomes (8).

Federal Reserve Board data on the 1949 income of spending units headed by retired persons provide additional information on the sources of those incomes. From 73 to 79 per cent had no income from employment or investments, and 28 per cent received no pension or allowance. The amounts received from each source were usually small. Of those earning wages or salaries, 13 per cent received less than $1,000, while 28 per cent of the units reporting income from investments received similar amounts. Finally, 46 per cent of the retired who were on pensions reported payments from that source of less than $1,000 (9).

The Institute of Life Insurance lists the following major sources of income for persons aged 65 and over. Percentages indicate the proportion of this group receiving income from the specified source (10).

	%
Employment	34
Pensions	18
Private assistance	17
Investments	9
Public assistance	22

SUMMARY. In general it may be said that, while about one-third of the older workers have incomes ranging from slightly below to considerably above the national average, the remaining two-thirds receive relatively small amounts of money annually. Within the group, the females and those living alone have the smallest incomes.

The data on sources of income for the older workers provide an insufficient basis for generalizations. They are limited in the age groups they consider, overlook many sources of income, and, finally, fail to take into account the extent to which older workers receive incomes from two or more sources. A study by the Bureau of Public Assistance estimates that in June, 1948, 10 per cent of all Old-Age and Survivors Insurance beneficiaries also received Old-Age Assistance payments, while another 7 per cent qualified for supplemental payments under the Aid to Dependent Children provisions of the Act (11).

Net worth of older workers

Another important factor affecting the economic status of older workers is their net worth. For most older workers this factor is significant only in terms of the amount of cash they can realize from the sale of assets. Their holdings are usually too small to be of much value as a source of investment income. This is evident from a comparison of older workers' net worths with the cost of lifetime incomes from annuities purchased from insurance companies. For example, a $100 a month annuity costs a male, age 60, approximately, $19,000. At age 62, the cost is $17,500; at 65, it is $16,000. Looking at this another way, a deferred annuity paying $100 a month beginning at age 65 requires payments of $25 a month for the thirty years preceding maturity. If payments are begun at age 45 or 55, they must be made at the rate of $44 and $106 a month, respectively (12).

The studies of net worth of the aged are incomplete and, in places, somewhat contradictory. One study, the Federal Reserve Board's "Survey of Consumer Finances", found that one-fourth of the consumer spending units headed by retired persons had net worths under $1,000. Similar valuations were reported by 21 per cent of the spending units headed by persons aged 45 to 54, by 22 per cent of those headed by persons aged 55 to 64, and by 27 per cent of the units headed by persons aged 65 and over. The survey also reported that from 54 to 59 per cent of the units headed by people in these three age groups reported net worth valuations in excess of $5,000 (13).

In contrast, a Federal Security Agency study of the net worths of Old-Age and Survivors Insurance beneficiaries reveals a range of median positive net worth valuations from $300 in three Southern cities to $3365 in

12 middle-sized cities in Ohio. The study, a compilation of 5 surveys made in different areas, revealed further that from 17.5 to 41.8 per cent of the male primary beneficiaries interviewed reported zero or negative net worth valuations. An additional 13.3 to 19.7 per cent claimed net valuations under $1,000 (14).

The conflicts in these data cannot be reconciled until more comprehensive studies are made. Future inquiries should attempt to overcome the shortcomings of the existing data. For example, an external check revealed the Federal Reserve Board findings substantially understated consumers' liquid assets. Both studies failed to consider such important assets as holdings of currency, bonds other than United States government securities, household possessions, and reserve value of life insurance policies.

*Older workers' propensity to save or dissave**

Another indication of the economic status of older workers may be found in the extent to which that group saves or dissaves. The Federal Reserve Board survey indicates that, while spending units with heads age 65 and over comprised 12 per cent of all spending units in 1949, they accounted for only 8 per cent of total positive savings for that year. In that same year, this group accounted for 10 per cent of total negative savings and 4 per cent of all net savings. Of the spending units headed by retired persons, 50 per cent reported some positive savings, while 24 per cent reported zero savings, and 26 per cent reported negative savings (15).

Other estimates of the extent of dissaving among the aged are found in the Federal Security Agency's survey of Old-Age and Survivors Insurance beneficiaries. Median amounts dissaved by male primary beneficiaries varied from $200 to $238 per year. It must be remembered here that dissaving is limited by the amount of savings available to the beneficiaries (16).

Employment Experience of Older Workers

General trends

The Changing Structure of the Economy. Population growth has fixed a steadily rising upper limit upon the number of people available for work. However, employment practices and socio-economic policies have increasingly reduced the size of this potential labor force as average age has risen. Community sentiment has come to regard retirement during the later years as desirable in itself thus limiting further the number of older people available for work. Finally, the transition from an agricultural to a

* As used here, saving and dissaving refer to the difference between current income and expenditures for current consumption. When expenditures for current consumption exceed current income dissaving or negative saving is said to take place.

locus of economic opportunities away from rural areas and into the expanding urban communities. The movement of the population has paralleled this shift. In the decade of the 1920's, about 8 million people moved into the nation's cities from rural areas. The migrants were largely young people, over 75 per cent of them ranging from 5 to 25 years of age. Only 9 per cent of those age 50 and over living on farms in 1920 moved to the city in the ten years that followed (25).

SUMMARY. These broad social and economic trends exert unequal and even opposite effects upon employment opportunities for older workers. A few changes emerge as unqualified gains for those age 45 and over. For example, our growing ability to produce more with less effort has brought about a substantial reduction in the average number of hours worked. In 1870, the average work week was 66.3 hours; by 1940 this had fallen to 43.0 hours. The shorter work week has undoubtedly made it possible for many ageing workers to remain in active, full-time employment for longer periods.

For the most part, the influence upon employment opportunities for older workers of the factors noted above is not clear. To begin with, the impact of given changes in our economy varies. World War II increased the hiring of the elderly in many occupations and industries. While there is some evidence to indicate this trend has slowly been reversed since the cessation of hostilities, the end effect of this experience is not yet known.

The protection from cyclical and other unemployment afforded older workers by length of service considerations cannot be evaluated without more extensive data on the extent to which the elderly are also long-service employees.

Similarly, the studies seeking to relate size of firm and age of industry to employment experiences of the aged are still too scattered to warrant appraising the effects of these factors on the group as a whole.

Finally, no attempt has been made to relate the age-incidence of migration within the United States to the employment experiences of older workers in any regions.

Perhaps the best single measure of the total effect of these conflicting forces upon the employment of older workers is the extent to which the elderly have remained in the work force. The increase in total population since 1890 has been accompanied by a lesser growth in the number of workers 45 and over in the labor force. In other words, older workers have become relatively less important as producers. This effect has been concentrated among the older males in the population, in particular among males age 65 and over. Female labor force participation has increased for the entire 45 and over group (26).

Some specific employment hazards confronting older workers

COMPULSORY RETIREMENT. The adoption of policies compelling retirement at some chronological age has been termed "the greatest of the hazards now faced by older workers" (27). These policies have their greatest incidence upon the group aged 65 and over. Significantly, this is the group for which participation in active employment has declined the most in recent years.

Attitudes toward compulsory retirement. There are various proponents of compulsory retirement. Many employers assert it bolsters the morale and efficiency of their work forces. Younger workers regard it as a means for creating opportunities for promotion. One study indicates that high and middle income employees also favor such policies.

On the other hand, doctors and psychiatrists almost unanimously agree premature retirement hastens physical and mental deterioration and death (28). A substantial number of employers are of the opinion that retirement at some arbitrary age robs them of skilled employees whose production they cannot afford to lose. Finally, older workers who are able to stay on the job feel such policies are unjustly discriminatory.

Other arguments for compulsory retirement at a specified age include:

1. A policy of this kind is easy to administer.
2. It permits management to plan its replacements more definitely.
3. It facilitates individual preparation for retirement by establishing a fixed date on which the transition from employment to some other activity is to be made.

Extent of compulsory retirement. No comprehensive data are available on the extent to which employees are forced to retire upon reaching a specified age. A 1948 survey of New York State employers revealed that 72 of 176 responding firms enforced some arbitrary retirement age. For the majority, the upper limit was set at 65 (29).

There is some evidence to indicate formal pension plans affect retirement policies. The New York study cited above found the percentage of compulsory retirement policies was twice as high among firms with pension plans as among those without such plans. A Minneapolis survey found the number of firms retaining able employees after 65 was almost three times as great among those without pensions (30). Other data on pension plans throw additional light on retirement policies. A 1940 survey of 347 pension plans found that, in all but 114 cases, provisions were made for employees' remaining in service after reaching the normal retirement age (31).

More recently, union efforts to establish pension plans through collective bargaining have affected retirement policies in organized industries.

Labor organizations have almost invariably opposed the incorporation of compulsory retirement provisions in the new plans. How effective their opposition has been is not readily ascertainable from the available data. Among the policies agreed upon by unions and managements in various industries are the following:

1. *Rubber industry:* employees may work until they are unable to fulfill their usual jobs or qualify for transfer to another job.
2. *Steel and aluminum industries:* employees may work until they are unable to fulfill their usual jobs.
3. *Carpet industry:* employees must retire at 68 if the employer and union so agree, or at 72 unless the employer decides otherwise.
4. *Automobile, farm equipment, and glass industries:* employees must retire at 68. Some plans permit employment thereafter at the employer's discretion; others permit involuntary retirement at 65 if the employee is unable to work efficiently.
5. *Locomotive manufacturer:* employees may continue in service after 65 only with consent of the employer.
6. *Railway equipment company:* employees must retire at 65 (32).

Two other studies corroborate this trend away from compulsory retirement policies in negotiated pension plans. Of 60 such plans in force in New York State in 1950, only 21 provided for mandatory retirement. In 12, the age limit was set at 65; in no case did it exceed age 70. Almost every plan gave the employer some discretion in invoking the mandatory rule (33). In a second study, the Equitable Life Assurance Society of the United States found that 150 of 355 of its clients made retirement mandatory at the normal retirement age. Although 70 of the respondents indicated exceptions to this rule were possible, they stated also departures from the rule were against general company policy and were rarely made (34).

Finally, other pension data indicate compulsory retirement policies are most prevalent among larger firms as shown in table 1 (35).

Effects of compulsory retirement. It has been estimated that if, in August, 1949, all members of the work force age 65 and over had been forced to retire, the number of producers in the nation would have fallen by over 3 million. The cost, in gross national product lost, would have been about $11 billion at 1949 prices. What has been the cost of our more limited adoption of compulsory retirement policies?

Experience with federal and private pension plans indicates a substantial number of older workers continue in active employment after they have qualified for benefits under their respective plans. The Federal Security Agency reports the proportions shown in table 2 of eligible primary beneficiaries as receiving benefits under Old-Age and Survivors Insurance (36). The average age of all retirants is 69.

Similarly, the Railroad Retirement Board reports that only [illegible] 20 per cent of insured workers retire within six months of reaching [illegible]. The average age of all voluntary retirants on the railroads is [illegible].

Experience under the new industrial pension plans is limited [illegible] of their recent adoption. However, fragmentary data indicate [illegible] 80 per cent of the steel and auto workers eligible for retirement are remaining

TABLE 1

Percentage of companies with pension plans [illegible]

Size of establishment	[illegible] pension plans	[illegible]	[illegible]
Under 250 employees	81	41	[illegible]
250-999 employees	138	44	[illegible]
1,000-4,999 employees	111	55	49.5
5,000 and over employees	50	27	54.0
Total	380	157	41.3

Source: National Industrial Conference Board, Handbook on Pensions, Studies in Personnel Policy, No 103, 1950, p 50

TABLE 2

Proportion of fully insured persons, age 65 and over, receiving monthly old age insurance benefits, 1941–1950

Year	Per cent	Year	Per cent
1941	20	1946	35
1942	29	1947	43
1943	31	1948	48
1944	30	1949	52
1945	30	1950	59

Source, Margaret L Stecker, "Beneficiaries Prefer to Work," Social Security Bulletin, Vol 14, No 1, January, 1951, p 16

on the job. The following companies report their experience as indicated (38):

U S Steel	About 40 per cent of those eligible are retiring.
Allegheny-Ludlum	Only 27 4 per cent retiring in 1950; average age, 69
General Motors*	Only 10 per cent of eligibles have retired, proportion is expected to increase sharply.
Ford*	About 43 9 per cent have either retired or applied for pensions.
Chrysler*	Over 11 per cent have retired

* Many of those retired had been drawing sick benefits and asked to be separated so as to qualify for larger pension payments

Taken together, these figures show conclusively that those continuing in active employment after age 65 outnumber those retiring. However, they say nothing about the extent to which retirants were, in fact, no longer able to work efficiently. The data in table 3 indicate that the percentage of older workers unable to work does not become significantly large until much later than age 65 (39). It may be that many of those retired involuntarily had, for some time prior to their retirement, been incapable of performing satisfactorily but had been kept on the payroll until they could qualify for pension benefits. There is some evidence that this is not uncommon when the older worker has been in his company's service for many years.

Federal Security Agency studies of why old-age insurance beneficiaries

TABLE 3

Participation of the male population 45 years and over in the labor force, April, 1940

Age group	Per cent in labor force	Per cent not in labor force	
		Unable to work	Other
45 to 54	92.8	5.4	1.9
55 to 59	88.5	8.2	3.3
60 to 64	79.6	14.2	6.2
65 to 74	51.6	34.7	13.8
75 and over	18.3	65.6	16.1

Source: John Durand, The Labor Force in the United States, 1890–1960 (New York: Social Science Research Council, 1948) p. 33.

retire have attempted to evaluate the effects of compulsory retirement. The results, summarized in table 4, clearly indicate that the motives underlying retirement vary directly with general economic conditions. This is shown by changes in the ratio of those losing their jobs to those retiring voluntarily.

As the economy approaches a high level of employment, employers become less prone to invoke compulsory retirement policies for their older workers. Similarly, rising wage rates and earnings improve the economic positions of aged employees, causing them to revise upward their estimates of the value of leisure. The result is a fall in compulsory retirements and a rise in voluntary retirements. However, when continued full employment is accompanied by a rising price level, older workers increasingly prefer to remain on the job, and even return to active employment if they have already retired (40).

Other evidence on the impact of compulsory retirement is scattered, if not lacking entirely. Whether such policies actually improve the efficiency

and morale of the work force is not known, although the belief that they do so is widely held. It is conceivable that, in a firm employing many older workers, mandatory retirement could adversely affect morale. As to the effects on efficiency, an adequate program for evaluating employees' performances and placing them on jobs in which they are likely to do well would provide a better solution of the problem of "hidden pension costs" than arbitrarily retiring all workers above some specified age.

There is little doubt that hastening the retirement of supervisory employees opens up opportunities for promotion to younger men. However,

TABLE 4

Reason for termination of last covered employment before entitlement, male old-age insurance beneficiaries in 20 cities, 1940–1947

Reason for job termination	1940 entitlements, 7 large cities*	1941–42 entitlements, 12 middle-sized cities†	1944 entitlements, Boston	1946–47 entitlements, Philadelphia and Baltimore
Number	2380	567	341	218
Total (*per cent*)	100.0	100.0	100.0	100.0
Lost job	55.7	46.2	25.5	53.2
Quit job	44.3	53.8	74.5	46.8
Health	33.8	41.1	64.8	34.9
Wished to retire	4.7	5.6	4.1	5.5
Other reasons	5.8	7.1	5.6	6.4

* Philadelphia, Baltimore, St. Louis, Birmingham, Memphis, Atlanta and Los Angeles. Includes January, 1941 entitlements in Los Angeles.

† In Ohio, population between 10,000 and 75,000.

Source: Margaret L. Stecker, "Beneficiaries Prefer to Work", Social Security Bulletin, Vol. 14, No. 1, January, 1951, p. 17.

the importance of this effect of compulsory retirement on mobility and

younger workers' obtaining employment at higher levels in firms other than the one for which they currently work.

Compulsory retirement policies facilitate the *planning* of personnel requirements. They are also easier to administer than selective retirement policies based on ability to perform the work. However, the lower administrative costs of compulsory plans must be balanced against any cost increases arising out of the greater turnover and loss of capable, skilled employees who are familiar with company procedures. The literature on

the older worker in industry does not indicate such comparisons have ever been made or are being made today.

Finally, unpublished data indicate that the belief that retirement causes physical and mental deterioration leading to early death is not substantiated by research findings. The Bureau of Employment Security and some insurance companies administering private pension plans have compared the incidence of mortality among employed and retired older workers. The investigators found no significant difference between mortality rates for the two groups within like age categories. It has been suggested the belief in question originated in and was perpetuated by the experiences of medical and psychiatric practitioners. These experiences were limited to cases wherein retirement had induced some adverse effects in patients. As a result, members of these professions have been prone to describe an atypical condition and apply it to the entire aged population. It is hoped that more studies will be conducted in this area soon, and their results made available to all (41).

LAYOFFS AND DISCHARGES. Unlike compulsory retirement policies, layoff and discharge practices in industry appear to favor older workers. Although the importance of this factor to the employment of older workers has not been measured statistically, the evidence indicates it is not insignificant in the total situation.

Impact of collective bargaining. The growth of labor organizations during the last two decades has led to greater acceptance of seniority as the criterion governing layoffs and discharges. The depression of the 1930's made workers extremely conscious of the implications of job tenure. This is clearly seen in comparisons of trade union agreements negotiated before and after 1930. In one such study of 388 contracts negotiated between 1923 and 1929, 117, or 30.2 per cent, controlled layoffs through some form of seniority, while 62.6 per cent were silent on that matter. However, of 400 agreements negotiated between 1933 and 1939, only 27.5 per cent failed to regulate these management decisions, while in 60.5 per cent of these contracts, some form of seniority governed layoffs (42).

A detailed analysis of seniority provisions is inappropriate here. All are equally limited in that the protection they afford older workers depends upon how closely age correlates with length of service within the seniority unit. Recent surveys appear to indicate there is positive correlation between these two variables as shown in table 5 (43).

These results cannot be accepted without reservations. The surveys assume that the unit of seniority is the employer. This is not always the case. One study found that 26 per cent of 242 trade union agreements negotiated between 1933 and 1939 provided for a seniority unit smaller than the employer or individual plant, while 100 contracts failed to define

the unit in their seniority clauses (44). Where workers hold seniority in some area smaller than the employing unit, their length of service with the employer is irrelevant to the protection afforded by the seniority agreement.

Secondly, the data do not indicate whether supervisory employees have been included in the averages. The job tenure of these management personnel is seldom governed by seniority provisions affecting non-supervisory workers. They are usually older and have longer service than the rank and file workers. This is revealed by a Rochester study made in 1948. Supervisors with the rank of foreman and up averaged 45.5 years and 16.7 years in age and length of service, respectively. The corresponding averages for clerical and salaried employees were 32.2 years and 7.2 years

TABLE 5

Length of service of 220,079 employees in New York State

Age	*Average years of service with present employer*
Under 21	1
21–40	5
41–50	10½
51–55	13
56–60	14
61–65	16½
Over 65	17¾

Source: Albert J. Abrams, "Industry Views Its Elderly Workers", Birthdays Don't Count, New York State Joint Legislative Committee on Problems of the Ageing, *Legislative Document No. 61*, p. 152.

while hourly rated factory employees averaged 37.1 years in age and 7.3 years in length of service with their employers (45).

Finally, no survey relating age to seniority considers the dispersion of employees about the length of service averages for each age group. Data on cyclical and seasonal fluctuations in the age composition of the labor force and the prevalence of business failures in the economy suggest chronic unemployment is common among older workers. If this is true, many of the aged members of the labor force are relative newcomers in their firms and will be adversely affected when layoffs and discharges are made in accordance with seniority. Further study in this area is needed to appraise fully the value to the older worker of seniority provisions in collective bargaining agreements.

Other length of service considerations. Apart from negotiated seniority provisions, employers appear to attach much weight to length of service in all personnel decisions. Pension studies indicate that, in the absence of formal retirement plans, managements feel strongly obliged to make some

provisions for their older employees who have been with them for many years but are unable to continue in active employment. A 1938 study found that of 24 New England firms hiring a total of 30,000 factory employees, only 3 had formal pension plans. Nevertheless, "nearly all were paying some form of pension to a few superannuated employees" (46).

Two surveys of employment conditions in New York State found the old, long service worker can be virtually certain he will not be discharged or laid off when employers reduce their work forces. This conclusion was advanced for both unionized and non-union firms. The investigations were made in 1933 and 1948, years of widely differing economic conditions (47).

Similarly, an examination of arbitrators' decisions in cases involving disputed discharges for cause reveals "... it is probably true that what is just cause for discharge varies roughly with seniority". Although the collective bargaining agreement may provide no basis for the distinction, "there is a rather general feeling (among arbitrators) that a worker who has spent many years on his job has some stake in that job and in the business of which it is a part, and that this interest should not be lightly cast aside" (48).

It is difficult to assess the net effects of seniority agreements and other length of service considerations upon employment opportunities for older workers. Statistical studies of employers' experience under unemployment compensation laws might provide a good index to the extent to which older workers are preferred over younger ones when work forces are reduced. More detailed inquiries into the relation between age and length of service would also be of value here. Until these data are available, little that is conclusive can be said about the quantitative effects of these factors upon older workers.

UNEMPLOYMENT AND AGE. Unemployed older workers are at a greater disadvantage than that attributable to a temporary loss of income resulting from changing jobs. This is due, in part, to differences in attitudes toward the employed and unemployed in the 45 and over group. Employed older workers encounter little or no difficulty in retaining their jobs until the later years, so long as they are efficient. On the other hand, for the unemployed, age is almost invariably a barrier to reemployment after 45; in normal times ability does not appear to influence this condition significantly.

Seniority and other length of service considerations also favor the currently employed over the unemployed older workers. This is most evident among railroad workers whose employment is rigidly governed by seniority (table 6).

A comparison of the participation and unemployment rates for older

workers within all occupational groups indicates that the factors determining whether older workers remain on the job differ greatly from those which determine whether unemployed older workers find new jobs. Without these differences, one would expect relatively low unemployment rates in those occupations where older worker participation is above average, and vice versa. Census data on participation and unemployment rates of older workers in the 12 major occupational groups in the nation's work force do not bear out this expectation (49)

Importance of self-employment. Of some significance to the incidence of

TABLE 6

Participation and unemployment rates in selected railroad occupations, 1940

Occupation	Participation rate*	Unemployment rate†
All workers, 45 and over	100.0	96.5
Railroad workers, 45 and over		
Conductors	240.4	102.9
Baggagemen, express messengers, railway mail clerks	154.7	83.0
Locomotive engineers	236.2	80.1
Locomotive firemen	132.5	93 2
Brakemen and switchmen	148.7	77.2
Laborers (including repair shops)	101.9	91.2

* Ratio of percentage of persons 45 years of age and over of the total experienced labor force in each occupation to similar percentage for all occupations in the experienced labor force.

† Ratio of the percentage unemployed in the total experienced labor force 45 years of age and over to the similar percentage unemployed of all persons in the experienced labor force.

Source: U. S. Bureau of the Census, 16th Census, 1940, Population, "The Labor Force" (Sample Statistics), Usual Occupations, Tables 4, 7, and 11.

unemployment upon older workers is the moderating effect of self-employment. This factor is most important for the older age groups in the labor force. Its influence is reflected in census data on the extent of unemployment in 1940. During that year, 19.2 per cent of the wage and salaried workers aged 45 and over in the experienced male labor force were unemployed. In contrast, only 2.3 per cent of the self-employed in this age group were not at work (50).

An examination of opportunities for self-employment among occupational groups shows that the importance of this factor differs for employed and unemployed workers. Where there is a relatively high proportion of self-employment in an occupation there also tends to be a high proportion of older workers in that occupation. However, few occupations contain

sufficient opportunities for self-employment to affect materially unemployment rates among all older workers in the field (51).

The importance of this mitigating factor to older workers is limited further by its declining significance in our economy. In countries like Canada, the shift from agriculture to manufacturing has been less complete than in the United States. Since opportunities for self-employment are most common in agriculture, unemployment among older workers is less severe in these countries than in the United States. Thus, only two per cent of Canada's 1,500,000 workers (males and females) aged 45 and over were unemployed in 1949; about 85 per cent of the 1,400,000 males in this group were own-account farmers (52).

Frequency of unemployment among older workers. The data tend to understate the frequency of unemployment among older workers. By considering current members of the labor force only, they fail to include those older workers who have dropped from its ranks unwillingly after repeated failure to obtain employment.

Census figures on the age-incidence of unemployment in 1950 show that this condition is most prevalent in the youngest age groups. While only 5 per cent of the entire labor force was out of work in that year, 10.8 per cent of those 14 to 19 and 7.2 per cent of those 20 to 24 were unemployed. Only 4.0 to 4.5 per cent of those aged 45 and over in the labor force in 1950 were jobless (53).

Perhaps a more meaningful estimate of the age-incidence of unemployment may be made by considering only the experienced members of the labor force. Obviously, nearly all of the inexperienced will fall within the youngest age groups. One study found that 97 per cent of the unemployed men and 91 per cent of the unemployed women who had never worked before were under 25 years of age. Separating these groups out of the total labor force raised the average age of unemployed males from 34.4 to 38.9 years, and that of unemployed females from 24.2 to 29.2 years (54).

Cyclical and seasonal forces affecting the general level of employment in labor market areas have a unique effect upon older workers. The data indicate that as unemployment increases, its frequency among older workers increases more rapidly. This was shown in a Bureau of Employment Security study of unemployment in six labor markets where varying labor supply conditions prevailed. The investigators found also that, while the unemployed accounted for 5 per cent of the total labor force studied, they represented the following percentages within the older worker group:

	%
Age 45 to 54	3.7
Age 55 to 64	4.1
Age 65 and over	4.7 (55)

Duration of unemployment among older workers. Differences in the age-incidence of unemployment are most apparent in comparisons of the average duration of unemployment for older and other workers. Older workers remain unemployed longer, on the average, than younger ones Table 7 summarizes the results of a Bureau of Employment Security survey covering 312,000 workers who were seeking jobs in early 1950. It may be noted

TABLE 7

Job applicants seeking work under four and over twenty weeks as a percentage of all applicants in age group by area

Age group	Houston (3-5% unemployed)	Lancaster (3-5% unemployed)	Columbus [illegible] unemployed
	Under 4 weeks		
Total	22.1	26.6	24.3
Under 20	35.6*	33.1	33.7
20 to 24	26.3†	32.2	27.5
25 to 44	23.0	28.7	26.1
45 to 64	16.2	24.7	18.8
65 and over	7.5	14.6	18.0
	Over 20 weeks		
Total	10.1	15.4	17.5
Under 20	5 3*	8.1	11.4
20 to 24	8.6†	9 8	10.5
25 to 44	8 6	13.1	17.2
45 to 64	13.3	19.1	22.4
65 and over	26 8	24.9	23.4

* Includes applicants under 21 years of age.

† Includes applicants 21 to 24 years of age

Source: "Employment Services Survey Job Prospects of Older Workers", The Labor Market and Employment Security, May, 1951, p. 18.

that the number of short-term unemployed falls consistently with age, whereas the long-term jobless become more numerous in the higher age groups (56).

Cyclical, seasonal and other factors that increase unemployment in labor market areas appear to aggravate older workers' inability to obtain reemployment over long periods of time. This is the finding in a recent survey of 100 major labor market areas. The investigators related the percentages of public employment service applicants seeking work for 20 or more weeks to the extent of unemployment in the labor markets. They

found the proportions of the long-term unemployed of all ages rose steadily with general unemployment. Classifying the applicants by age revealed the incidence of long-term unemployment was greatest for the older workers regardless of the extent of unemployment (57).

Obstacles to Reemployment for Older Workers. *Beliefs about productivity of older workers.* A great number of "opinion polls" have been taken among employers and others concerning the employability and performance of older workers. Although the tabulations of responses usually provide no objective basis for evaluating older workers, they do reveal significant insights into the beliefs held by those polled.

The answers received by the New York State Joint Legislative Committee on Problems of the Ageing are fairly representative of those usually given. Employers in the state asserted they did not hire older workers because:

1. Workmen's compensation rates go up when the elderly are employed.
2. Older workers are subject to higher accident rates and endanger other workers.
3. The public prefers younger workers for jobs requiring public contacts, such as waitresses, clerks, office workers, salesmen, etc.
4. Elderly workers cannot produce as efficiently as younger workers.
5. It is unprofitable to invest in the training of an older worker (58).

Hiring age restrictions. The beliefs about the declining productivity of older workers frequently give rise to formal and/or informal restrictions on the ages of new employees. The stringency with which these restrictions are applied varies with changes in labor market conditions. War emergencies, partial mobilization, and normal prosperity make for "tight" labor market conditions impelling employers to relax job specifications when seeking new employees. Age restrictions on retirement and hiring are overlooked under these circumstances. A recent study analyzed job orders placed with the public employment service in six cities. Labor market conditions in the areas varied from "tight" to "substantial surplus". It was found that the percentage of job orders without age restrictions varied from 53 per cent where the labor supply was "tight" to 32 per cent where there was a "substantial surplus" (59).

Tabulations of formal age restrictions on hiring substantially understate the extent to which unemployed older workers are at a disadvantage. A 1933 survey of unemployment in New York State found that 40 per cent of the manufacturing jobs investigated were covered by formal maximum age policies, while an additional 19 per cent were under informal restrictions of this kind (60). An earlier survey of about 2,500 firms discovered that, although only 7.5 per cent reported formal hiring age limitations, 38.8 per cent of the companies without such policies gave preference to

applicants under 40. Some indication of the impact of all maximum age restrictions upon older workers may be had from the fact that of 651,930 new employees hired by 750 of these companies in 1937, only 8.4 per cent were over 40 years of age (61).

Comparisons between the age composition of the employed members of a work force with that of the population from which they are drawn provide the most significant measure of the effects of hiring age restrictions. Applying this method to a 1930 survey of hiring practices in Baltimore, Maryland, the writers found the survey results gave an inaccurate picture of the true state of affairs. Responses to questionnaires indicated maximum hiring ages were being enforced by only one tenth of the firms contacted. These companies employed 35 per cent of the labor force then at work. The maximum most commonly reported was age 45.

The writers compared the ages of workers in 7 retail department stores and 56 manufacturing establishments with the age distribution of the population of the city as a whole. The comparison revealed that, in retailing, the unemployed were adversely affected after age 30, and, in manufacturing, after age 35. The size of the differences between age distributions among the employed and the population indicated a degree of discrimination greater than that shown by the questionnaires (62).

Conclusions. The data on employment experiences of older workers suggest the following are indispensable pre-requisites for improving the utilization of this segment of the labor force:

1. The general level of employment must be high.
2. Hiring must evolve into a practice of matching individual applicants' abilities with actual job requirements.
3. Unemployed older workers must remain sufficiently flexible to adapt to changing economic conditions and to changes in job demands.

Age, Employability and Productivity

Effects of Ageing on Employability. Beliefs about the employability of older workers have been subjected to varying degrees of rigorous examination by investigators in industry, government and the professions. These studies may be classified into two groups: those based on industrial production records; and those made in the laboratory.

Age and productivity. Existing knowledge of the effects of ageing on productivity is perhaps more deficient than in any other phase of the older worker problem. There is simply not enough information of the kind needed to formulate definitive conclusions. Adequate analyses would require: (a) output records by age, covering a substantial number of employees engaged in work of approximately equal difficulty; (b) the selection for study of jobs in which speed is governed by the workers themselves;

and (c) performance records covering a period long enough to permit making significant averages for each age group.

One such study examined the productivity of 172 textile weavers, 127 textile spinners, and 147 nonferrous metal workers for whom adequate data were available. The investigators could find "no pronounced tendency for productivity to vary with age" (63). This conclusion appears to contradict what might be expected on a priori grounds. It seems more plausible that workers' physical capacities deteriorate with age, causing their productivity to fall off. Of course, this tendency would not be expected to affect all older workers equally, and it may be that considerable individual variations lie behind this apparent paradox.

Production statistics tend to be biased in that they usually include only those workers whose performances are satisfactory. Thus, if the inefficient workers eliminated in the selection and placement processes were composed of disproportionate numbers of the aged, production data would not portray accurately the distribution of productivity among age groups. Such data are also biased by the tendency for promotions based on ability to be given more often to older than younger workers. Finally, it may be misleading to imply that output is synonymous with total ability to produce. It is probable that few jobs require workers to do their utmost. If this is so, any study of productivity variations between age groups would have to determine how these untapped reserves differ with age among workers producing at comparable levels.

Age distribution data provide a second source of information on the influence of age on ability. When properly constructed, these analyses show the frequency of satisfactory performances among age groups. Age distributions permit comparing workers in jobs on which individual production records are difficult to compile. Figure 1 illustrates graphically the type of analysis that appears most fruitful. Note the significant percentages of older workers in jobs requiring above average amounts of each factor, e.g.:

Mental effort	32 per cent in jobs requiring above average amounts.
Physical effort	43 per cent in jobs requiring above average amounts.
Health hazards	45 per cent in jobs with above average amounts of these present.

Unfortunately, the study from which the data were taken did not include the distribution of workers under 50 years of age. The job evaluation technique used followed that of the National Metal Trades Association (64).

A second study of this kind examined the age distribution of workers performing 100 different operations in 24 plants. The investigators found jobs emphasizing speed were most often done by younger employees,

whereas those ... great accura... employees. The older workers were ... but this may have been a secondary ... speed is more easily adjusted in the ... difference between the age distribution ... such as machine feeding, light assem... payment (65).

Industrial ... and other...

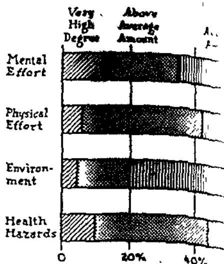


FIG. 1. *Percentage distribution of fact... levels of effort and working conditions of ... condition.*

Source: Harry Machaver, The Utilizatio... Study at the Ithaca Gun Company, table ... M.S. thesis, Cornell University, 1940).

ments to determine the influence of ... but a few of the findings, it has ...

1. Older people are slower at organ... it in terms of new tasks.
2. *Older people generally tend to ...*
3. Differences between individual ... age.
4. Industrial skills can be maintain... which they can be learned with ... ing methods.
5. Older people work more happil... small rather than large groups ...

did require somewhat more at- ...mployees (69).

Apart from the allegation that ...han younger ones, the argument ...kers raises workmen's compensa... ...r. *Henry D. Sayer, General Man-* ...n Insurance Rating Board, said: ...he employment of older workers ...ly a misconception" (70).

...*ome factual basis. Older workers* ...*es than younger ones* With the ..., employers hiring older workers ...ion costs when some became per... ...nsable illnesses which might have ...en employed However, in recent ...een amended by "second injury ...ility to the extent provided for ...imbursed for additional damages ...covered employers. By 1950, 41 ...mpensation laws in this fashion

...senteeism for causes other than ...t only those able to maintain rea... ...n active employment. Few studies ...e and some of the results appear *found that absenteeism decreased* rates for women of all ages were ... It is conceivable that the young... ...few responsibilities, would be the ...lder people's greater proneness to ...*eeism for this reason alone* would ... has revealed about a third of ...and Survivors Insurance pro... ...iling health (74).

...*illness among employees* ... Average annual num... ...*ge until 55, after which* ...er of days per absence ... the 55 year mark was ... *absent per person also* ... years of age (75). ...e of costly ...

6. Studies of performance must consider methods changes which tend to be associated with changes in output.
7. Measuring simple motor or sensory functions has little meaning for predicting performance in complex industrial jobs. Such jobs allow workers to use more than one method (and physical function), and seldom exhaust their capacities (66).

Age and industrial accidents. It is commonly alleged that older workers are poorer accident risks than younger ones. Studies here are spotty and subject to the same selective influences characteristic of all industrial employment data. Perhaps the greatest deficiency in the available data is the lack of information on the extent to which workers are exposed to accidents. Also, they offer no indication of the extent to which older workers are deliberately placed in less hazardous jobs.

A 1939 investigation of the frequency, severity and costs of accidents in relation to age in two large New England plants concluded, "the divergent experience of these firms indicates the importance of further study before conclusions may be safely drawn". In one company, the frequency, severity and direct costs of all accidents rose with age; in the other the reverse was true. Accident costs per employee were so low in both firms that the investigators concluded, "the cost of accidents in such firms does not constitute a convincing reason for favoring any age group in developing employment policies" (67).

A more comprehensive study, published a year later, corroborated the tendency for accident frequency to decline with age. Evidence from the records of four large manufacturing firms, from the city of Milwaukee, and from the International Labor Office covering industrial accidents in Switzerland and Austria all bore out this trend. However, injuries resulting in death or permanent impairments increased in frequency with age. This was true for both men and women workers, although the curve of male fatalities lay considerably above that for females. Finally, older workers, on the average, required longer healing periods for recovery from non-fatal accidents. The investigators stated: "It is an open question, still to be verified by study, whether the less frequent but more severe injuries to older workers are more or less costly than the more frequent but less severe industrial injuries to younger workers" (68).

Succeeding investigations do not appear to have uncovered any evidence substantiating the opinion that hiring older workers increases production losses from accidents. A two-year study of the employment records in 109 plants found that older workers suffer disabling injuries only a little more frequently than those aged 25 to 44. The average number of days of disability from such injuries increased steadily with age. On the other hand, older workers suffered non-disabling injuries less frequently than their

younger fellows, although their injuries did require somewhat more attention than did those of the younger employees (69).

Age and workmen's compensation costs. Apart from the allegation that older workers are more accident prone than younger ones, the argument is frequently raised that hiring older workers raises workmen's compensation costs. Commenting on this belief, Mr. Henry D. Sayer, General Manager of the New York State Compensation Insurance Rating Board, said: "If employers are of the opinion that the employment of older workers affects their insurance rates, it is certainly a misconception" (70).

At one time this belief may have had some factual basis. Older workers are usually more prone to chronic illnesses than younger ones. With the passage of workmen's compensation laws, employers hiring older workers ran the risk of incurring high compensation costs when some became permanently disabled by accidents or compensable illnesses which might have been less costly had younger workers been employed However, in recent years, state compensation laws have been amended by "second injury provisions" limiting the employers' liability to the extent provided for the most recent injury. Employees are reimbursed for additional damages out of a special fund supported by all covered employers. By 1950, 41 states had amended their workmen's compensation laws in this fashion (71).

Age and absenteeism. The data on absenteeism for causes other than accidents are also biased by the fact that only those able to maintain reasonably good attendance records remain in active employment. Few studies of absenteeism and age are available here and some of the results appear to conflict. For example, a recent study found that absenteeism decreased with age, regardless of the cause. The rates for women of all ages were about twice as high as those for men (72). It is conceivable that the youngest workers, because of their relatively few responsibilities, would be the least reliable in attendance. However, older people's greater proneness to long illnesses makes it unlikely that absenteeism for this reason alone would also decrease with age (73). Investigation has revealed about a third of the voluntary retirants under the Old-Age and Survivors Insurance program left active employment for reasons of failing health (74).

The findings in a study of absenteeism due to illness among employees of a large public utility bear out these expectations. Average annual number of absences per 1,000 employees declined with age until 55, after which the rate rose slightly. Average duration or number of days per absence rose steadily with age, increasing sharply after the 55 year mark was passed. Finally, average annual number of days absent per person also rose with age, nearly doubling for employees over 55 years of age (75).

Age and turnover. It is sometimes stated that, because of costly training

and other requirements, it is unprofitable to hire older workers whose remaining working life expectancies are relatively short. There is no doubt that young applicants have more working years ahead of them, on the average, than their seniors. However, this fact would be relevant only if an employer could be sure both the younger and older applicants would remain in his employ for the remainder of their working lives. There is, of course, no certainty about an employee's remaining with any employer. Therefore, evaluations of the profitability of training applicants of varying ages must consider the age-incidence of voluntary quit-rates as well as working life expectancies.

It is generally agreed that older employees remain on a job longer than younger ones (76). One study attributes this to:

1. The natural instability of youthful interests;
2. The search for vocational objectives characteristic of the early years of working lives; and
3. The absence, in youth, of economic and social responsibilities.

This inquiry found voluntary quit-rates decreased with age until a "critical period" beginning at 36 years was reached. During this period, separations rose again until age 50, after which stability of employment increased sharply with age. The investigator attributed the "critical period" to a probable reduction in the number of dependent children, coupled with the growing realization that further delay would make any contemplated job changes more difficult to accomplish (77).

Selective Retirement

In considering the application of selective retirement procedures within the older worker group, it is possible to distinguish three types of employees: one, those who are able to perform satisfactorily the duties of their usual jobs; two, those whose performances in current assignments have become sub-standard, but who are able to handle other jobs in the organization; and three, those whose capacities have been impaired to the point where continued employment at any job is uneconomic. An adequate selective retirement program must be able to identify these sub-groups among older workers in the firm. The program should also be an integral part of the personnel function. Lastly, it must look forward to the eventual retirement of all employees, assisting them in making the transition from active employment to a state of reduced activity and income.

Elements of a Selective Retirement Plan. The goal of the selective retirement program is the optimum utilization of the current work force and job applicants. The first requisite is adequate knowledge of the requirements of each job in the organization. This calls for job descriptions, analyses, and evaluations for the entire in-plant job structure. The extent

to which these should be formalized is probably a function of size of firm. Obviously, the personnel manager in a plant of 100 workers has more first hand knowledge of his job-structure than does his counterpart in a plant hiring 1200 or 1500 employees. Therefore, he has less need for detailed procedures of analysis than the latter.

Physical demands analyses. Regardless of the form in which job information is collected and evaluated, its minimum contents are the same. Attention here will be focussed on those elements most relevant to the employment of older workers. These are, in the main, data on the physical demands associated with the duties of each job and the environmental factors affecting performances. An example of the analysis referred to is that developed in a large shipyard during World War II

The physical demands of each job in the shipyard were divided into two groups: one, mechanical factors; and two, environmental factors. Twenty-five sub-factors were isolated under each heading. They were:

Mechanical factors

Lifting	Running	Crawling	Feeling
Carrying	Walking	Twisting	Talking
Handling	Standing	Reclining	Hearing
Pushing	Stooping	Sitting	Seeing
Pulling	Crouching	Reaching	Color vision
Climbing	Kneeling	Fingering	Depth perception
Jumping			

Environmental factors

Inside	Explosions
Outside	Vibrations
High temperature	Noise
Low temperature	High places
Sudden temperature changes	Cramped quarters
High humidity	Wet quarters
Low humidity	Working with others
Toxic conditions	Working around others
Radiant energy	Working alone
Moving objects	Day shift
Mechanical hazards	Swing shift
Electrical hazards	Night shift
Exposure to burns	

The description and analysis for each job included information on the extent to which each mechanical and environmental factor was present, e.g.: "Lifting.—lifts 25 pound 'bucking bar' chest-high 40 to 60 times an hour" (78).

Physical capacities analyses. The second essential element in the selective retirement plan is the physical capacities analysis for current employees

and applicants. It is assumed here that workers' abilities are identified either through some form of performance review for current employees or a type of pre- or post-employment investigation in the case of new employees.

Data on physical capacities are obtained largely through medical examinations. Although these are widely accepted in industry today, the information gathered in them is seldom in a form suitable for a procedure of the kind contemplated here. For example, in the shipyard mentioned above, before selective placement procedures were adopted, applicants were examined and classified into one of four categories:

1. Fit for any work.
2. Fit for moderate work.
3. Fit for light or sedentary work.
4. Fit for no work.

These classifications, while distinctly helpful, were obviously too ambiguous to give the placement officer the specific information and guidance needed to attain optimum utilization of employees.

Under the selective placement program, shipyard physicians evaluated physical capacities in terms of the mechanical and environmental factors used in the physical demands analysis. Physical impairments were expressed as maximum capacities for satisfying each job factor. The result was a detailed description of each worker's physical capacity that was comparable with specifications covering the physical requirements of the job. With these two sets of data before them, placement officers were able to make accurate judgments concerning the fitness of applicants or current employees in terms of job requirements.

Results with the selective placement program in the shipyard mentioned above were quite satisfactory. Although the management was not able to use the procedure with new employees, it found it to be of immeasurable value in reducing lost time from injuries on the job. Disabled workers were returned to active employment as soon as the analysis of their physical capacities showed they could perform some job in the shipyard, although not necessarily their usual one. In 18 months about 10,000 analyses were made. Most of these were for workers with orthopedic or cardiac disabilities. Among the latter, of 84 cases of coronary thrombosis, 56 were returned to work. Only 19 of these went back to their old jobs which in 11 instances were manual labor (79).

A second method of determining physical capacity necessitates compiling an achieved strength index for each applicant or employee. In the Rogers Physical Fitness Index this is done by testing arm strength, leg lift, back lift, left and right grips, and lung capacity. For example, arm strength

is measured by the formula:

$$\text{Arm strength} = (\text{push ups} + \text{pull ups}) \times \left(\frac{\text{weight}}{10} + \text{height} - 60\right)$$

The sum of test performances is compared with charts listing normal strength indices by sex, age and weight, and the individual's physical fitness index (PFI) is expressed as follows:

$$\text{PFI} = \frac{\text{Achieved strength index}}{\text{Normal strength index}} \times 100 \ (80)$$

A comprehensive medical program. The third element in a selective retirement program is an adequate, on-going medical program for all employees. In addition to pre-employment physical examinations, a program of this kind must include regular reviews of employees' physical conditions. Recent surveys indicate the percentage of business establishments using both pre-placement and periodic physical examinations is increasing. The cost of maintaining medical departments large enough to handle both functions has undoubtedly led to industry's emphasizing the periodic examination for special employee groups only, e.g. older workers (81). Thus, a firm may require employees under 40 to be examined once every five years, or perhaps at the employee's request; employees aged 40 to 50 may be asked to take such examinations semi-annually, with the requirement becoming annual after age 50.

It may be useful to consider briefly the nature of the industrial medical service as it relates to older workers. Available evidence indicates many of the disabilities workers encounter in their later years have their origins in chronic ailments contracted earlier in life and neglected until their symptoms become acute. Therefore, one of the primary goals of the industrial medical program should be the detection of latent illnesses which, if untreated, would cause excessive absenteeism and, finally, the loss of valuable employees. Detection, of course, must be accompanied by an efficient follow-up procedure. This should include periodic check-ups on the progress made in treating ailments, as well as provisions for employees' using, on the job, any protective appliances that are necessary for safety.

Preparation for retirement. The last element in the selective retirement program is a program of education for retirement. As yet, programs of this kind have not been adopted to any great extent in industry. However, the recent growth in the number of private pension plans has awakened much interest in them, and it is likely that their number will increase greatly in the future.

The basic idea behind preparing employees for retirement is an old one.

Surveys show that a majority of companies with retirement plans have made some attempts to prepare their prospective retirants for the change confronting them. However, in most cases, these efforts are highly informal. They are usually limited to a review of the employee's prospective retirement income; the interviewer does not discuss any personal problems the employee may have unless the latter mentions them. These efforts are frequently "one-shot" affairs, conducted six months or a year before retirement will take place (82).

Recently, several exploratory efforts have been made in industry toward developing more adequate pre-retirement educational programs. One firm has proposed a three-part program that includes physical, mental and financial preparation for retirement. The program will combine lectures and individual interviews in presenting the materials. Participation is limited to employees over age 45 and is voluntary. All sessions are held on company time and within the plant premises. The program includes:

1. Annual physical examinations beginning at age 45, becoming semi-annual at 55, with interim consultations where necessary.
2. Semi-annual lectures by medical personnel on the general aspects of health and ageing.
3. A series of 5 interviews, beginning in the twentieth year of service and ending one year before retirement; these are to be counselling interviews conducted by trained interviewers. They will cover personal problems, economic questions, and anything else relevant to obtaining an adjustment to retirement.
4. The expansion of company provisions for hobby and craft shows as a means of encouraging employees to develop leisure time activities (83).

A second firm secured the assistance of a University Extension Service to establish an experimental lecture-seminar program for its foremen. Participation was extended to the wives of the men electing to attend. Follow-up interviews were held with the participants to determine their reactions to the materials presented. The latter included discussions of financial security, physical and mental health, the psychological changes associated with retirement, living arrangements in retirement, and leisure time activities (84).

A third firm has begun a 5-meeting group discussion series for its older employees, oriented to the concept that retirement is "... a sort of 'graduation' into a new phase of life rather than a 'casting out' process" (85). The objectives of the series are:

1. To give each prospective annuitant a picture of the problems he is apt to face when he retires:

2. To stimulate organized thinking toward suitable post-retirement interests and activities; and
3. To generate some action on plans before retirement occurs.

It would appear that programs preparing employees for retirement, to be effective, should begin at least five years before the change takes place Where retirement is compulsory, the age at which it occurs is largely beyond the employees' control. In other instances, no optimum retirement age can be designated. Important factors affecting the decision to retire include individuals' sensing of declining physical capacities, and their desire to fulfill other interests (86).

Procedures in Selective Retirement Program. Applying the selective retirement program to the current work force is a two-step procedure involving: first, the review of employees' performances and the discovery of problem cases; and second, the disposition of problem cases

As noted before, size of firm will materially affect the form in which job information is collected and evaluated. The same observation is true for discovering examples of poor placements. This may be done informally through supervisors' observations of daily performances, or it may be accomplished through a formal merit rating and review procedure. Periodic medical examinations also reveal those instances where workers' physical capacities have fallen below the physical demands of their jobs.

Once identified, problem cases are referred to a review board for disposition. The personnel of the board will vary among firms according to their organizational structure, but, in general, it should include representatives from the production, medical and personnel departments. Three alternative decisions are open to this board in each case It may retain employees on their current jobs; it may transfer employees to other, more suitable jobs; or it may retire workers from active employment in accordance with a company pension plan (87). The first alternative necessitates tailoring the job to the worker; the second, matching the worker to existing jobs. The size and complexity of the in-plant job structure will undoubtedly determine which is more feasible.

When older workers are retained in their usual jobs. Several variations upon each of these alternative procedures are possible. For example, if an employee is to be kept on his regular job despite declining productivity, the wages paid him may be adjusted to conform with his reduced output. This may be done simply by reducing his current wage rate. The reduction may be accomplished through shifting the method of payment from an hourly to a production basis where this is possible. Or there may be a reduced rate, a superannuated pay scale, for workers unable to maintain output standards, such as that used in the printing trades. Where it is

possible to utilize those older worker characteristics which make them superior to younger workers, such as their greater accuracy, wage rates may be shifted from a production to an hourly basis. In rare instances, earnings based on production rates are supplemented up to a fixed minimum, and the additional cost is charged to some overhead account.

Retention on the same job may be accompanied by adjustments in work schedules also. Hours of work per day or days per work week may be reduced for older workers whose capacities are declining. Such short-time work schedules are often dovetailed to achieve a constant work force within departments. Where plant utilization is on a two or three-shift basis, it is sometimes possible to effect transfers to the easiest shift. The provision of frequent rest periods for older workers who are "slowing up" also facilitates their remaining on their usual jobs. These are seldom scheduled, but managements usually reserve the right to suspend the privilege when it is abused.

Finally, older workers who "slow up" may be retained on their usual jobs by adjusting the content of those jobs. This may be done by reassigning the more demanding duties to younger workers, by employing helpers to assist the older employees, or by developing special mechanical aids for the latter's use. Adjustments of this kind enable older workers to "taper off" gradually as they make the transition from active employment to retirement. Agricultural workers, particularly the self-employed, are able to do this very well, a fact that accounts, in part, for their longer working life expectancies (88). The organization of other forms of productive enterprise require special effort by management to make adjustments of this kind.

When older workers are transferred to other jobs. The second alternative open to the review board is transferring older workers to other jobs more suitable to their declining physical capacities. Several recent surveys indicate a majority of firms are now doing this in some fashion (89). The selection of jobs to which employees are transferred may be done informally, or it may be a part of a formal job evaluation procedure. Some large firms are able to establish "reservation jobs" within their organizations. These are less arduous positions, reserved for older workers and other employees who have definite physical limitations (90). The printing trades apply a system of apprenticeship in reverse to their older workers, moving them into less demanding jobs or "situations" at reduced pay as their abilities and capacities decrease.

When older workers are retired. The remaining alternative, that of retiring older workers, is used by the review board when employees' physical capacities have declined to the point where they are unable to handle any job in the organization. In such cases, retirement is compulsory. Before

this last resort is invoked, review boards should explore every possibility of retraining the employees to equip them for relatively sedentary jobs outside their usual occupations. A special effort to do this should be made for employees who are physically unfit to continue in active employment but too young to qualify for retirement benefits under the company or federal plan.

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ROLES AND STATUS OF OLDER PEOPLE

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On an island in the South Pacific there lives an old man. He is not loved by fellow residents of the village, not even by his fellow clansmen, although he helps them mightily in their continued competition with the rival clan that shares the village with them. They do not love him, yet they accord him a grudging respect because the old man is crafty, and, with his knowledge of sorcery, it is good to have him for a friend rather than an enemy. As he goes about the village from his solitary hut to the places of his work he is greeted with respect by old and young alike. When he has passed by, parents say to their children, "Show him respect, otherwise he may do you harm with his witchcraft," and they say among themselves, "How long will the old man retain his power? Not for long, possibly."

The time of a feast arrives, when the whole village collects in the central place, and there is story telling by the wise men of the rival clans, and each side tries to discover some of the secrets of the other, without disclosing the secrets of its own clan mythology. The old man takes a turn. He tells a story which shows to the rival clan that he knows one of their secrets. They try not to exhibit their consternation, but the people of his own clan recognize that he has scored a point and they shout their approval of his cunning. He is still a leader among them. At the close of the feast he is a little drunken with fermented liquor and he struts about the village with a lordly air. "See the ugly old man," the villagers say, "he still keeps his power."

In this village, the status of a man is what he achieves by hard work and shrewdness and what he retains by the ruthless use of his power. It is customary to say about such a society that status is *achieved*. If an old person has high status, it is because he has achieved it and he continues to act so as to retain it. When he loses his grip on the things that have

earned his status for him he will no longer be respected by the people. He will be just another useless broken-down old man.

On another South Sea island not a thousand miles from the first there is an old man who has just found himself to be one of the two head men of the village because a former head man has died and he is next in line for the post. This old man is a mild, rather stupid person and, if such a thing were conceivable, he would gladly resign his high-status position. The position comes to him automatically because he is one of the two oldest men who is married, his wife living, with at least one male and one female child, and no great-grandchildren.

All the major decisions of the village are made by him and his colleague in status, aided by the next eight men in line for his position, who form a kind of executive committee. When a difficult decision must be made, this old man is likely to avoid it if it can be postponed, thinking that perhaps the next head man will be able to act more wisely. But if the decision must be made, he makes it with the advice of the other elders and everyone in the village respects the conclusion. Even if it is a matter as serious as driving a young woman out of the village because she has broken a sex-taboo, her family will not hold it against the old man because, they say, "He is doing what must be done."

The people of the village have always known this old man as a friendly fellow, who looked after his children well but was not a good hunter. Now that he has moved up into the position of head man, they have not changed their attitudes about him as a person although they pay great respect to the position which he holds.

The high status of this man is said to be an *ascribed* status. It comes to him automatically, by virtue of what he *is*, not what he *does*.

Status in the American society is a mixture of these two types. To some extent it is ascribed. A child born on the "wrong side of the tracks" has a lower status ascribed to him by the society than a child born in a "better-class area". He does nothing to earn or achieve this status. An old person in the United States has a somewhat lower status ascribed to him than the status ascribed to a middle-aged person. Compared with the classical Chinese society, where the highest status was ascribed to the old man at the head of the family, the American old man has a considerably lower ascribed status. On the other hand, there are societies such as the Eskimo society of Labrador where old people have a very low status ascribed to them. In the struggle for existence that occupies the lives of those Arctic people, old people are a burden. They are expected to wander off quietly and die.

Old people in the United States have an ascribed status between these two extremes and closer to the higher end. But they are definitely lower

in status than the middle-aged. In addition, some of them achieve and retain high status, just as high status is achieved by younger people They work for it and they hold onto it. Hence there are great variations in status among older people due to their different levels of achievement A few even gain in status as they grow older.

The Concept of Role and Status

"All the world's a stage, and all the men and women merely players" Shakespeare was a perceptive student of society and we have him to thank for suggesting one of the most useful concepts of modern social science—the concept of social role. Life is a great complicated series of dramas, with a number of roles that are played over and over again by people of different nations and different centuries. Like the players in a stock company each person has a variety of roles. A woman may be a mother, a grandmother a wife, a church-woman, a citizen and a club woman. A man may be a father, a worker, a husband, a gardener, a citizen, a Rotarian, a golf-player.

In playing their roles people win or fail to win the applause of the audience—the community around them. They are happy if they win a fair measure of applause. Even if they merely plod through their roles without distinction they get the satisfaction of being in the play and of filling in their time with familiar routines. But if their performance is poor, or if they have poor roles to play, they feel the weight of the audience's disapproval and the sting of their own self-criticism.

For the purpose of this discussion, a role may be defined as a coherent set of activities which is recognized and judged by others as something apart from the individual who happens to fill the role. For example, a policeman in uniform is expected by everybody to behave in certain ways regardless of what kind of an individual he is. All policemen are alike in so far as they have a policeman's role. Similarly for Pullman porters, bankers, priests, waitresses and night club hostesses.

A particular role has a certain value or status in the eyes of the community. Consequently, a person who plays this role tends to be valued by others and to value himself in accordance with the status of this role. And, since every person plays a number of roles, his value or status tends to be more or less an average of the values of these roles.

But a person can rise above or fall below his role and be valued for what he is in spite of his role. For example, a certain banker or a certain doctor may be regarded in the community as a "poor excuse" for a banker or a doctor, while a certain odd-jobs man or a janitor may be regarded as a "first-rate person" in spite of his low-status role.

Thus, although an individual tends to be evaluated by society and to value himself at the level of the roles which he fills, this value that derives

from his roles is modified by his own individual qualities which are recognized by society generally and by himself as affecting his worth as an individual.

We now turn to a more careful definition of *status*, which is a key concept in this discussion. The status of a person may be defined as the general level of the community's evaluation of the roles he plays as modified by his own personal qualities. The status of a group of people is the general level of the community's evaluation of the characteristic roles of this group. Thus, the adults in our society have a higher status than the children, the rich a higher status than the poor, the middle class is higher than the working class and the upper class higher than the middle class. The college sophomores are higher in status than the freshmen. Middle age is higher than old age.

These illustrations immediately raise questions in our minds. Is the upper class *really* more valuable than the middle class? Are adults *really* more valuable than children? Questions of this type we cannot answer, unless we have some universally agreed standard of value. Our statements about relative status of the various groups represent what the people in our society generally say, or act as if they mean, concerning these groups. The attitudes of the public may be very uncertain and confused concerning the statuses of certain groups. For example, one is inclined to say that men enjoy higher status than women in our society, but many people would disagree, and certainly some of the roles of women—motherhood, for example—are valued more highly than almost any male role.

In any case, there can be little disagreement with the proposition that the period of highest status for a male in American society is the period of his middle adulthood, roughly from 30 to 60. If a professional baseball player or prizefighter has his highest status in his twenties, we know that this is unusual for men as a whole and we rather pity the former "great" when he is "on the shelf" at 40 or 50, and has dropped in status to the level of the common man. If a man rises from ordinary status to high political office in his sixties, again we recognize that this is an exception to the rule.

For women in America, the period of highest status is from 20 to 50. This is the period of child-bearing and rearing children, of looking one's best, of feeling that one is of most worth. After 50 the American woman must change her roles. She may become a grandmother and get a modicum of pleasure and feeling of usefulness out of helping with the grandchildren. Or she may go in for club work with an emphasis on community betterment. Or she may look for a job, not so much because she needs the money as that she needs to feel useful.

Thus the period after about 60 for men and about 50 for women is one of stress and strain in America, with loss of valued roles and a search for new roles which will be fairly satisfactory to self and society. This search must result in a measure of disappointment for nearly everyone in our society because the roles of later maturity usually are not valued as highly as the roles of middle adulthood. Consequently, as people grow older they often strive to retain the roles of middle age. They are complimented on their failure to grow old. At the same time, we are certainly ambivalent about older people. We think they ought to grow old gracefully—to accept and play gracefully the roles of old age—and, consequently, we tend to blame them for holding on stubbornly to the roles of middle age We both approve and disapprove their assumption of the roles of the elders

With this introduction to the concepts of role and status we now turn to a consideration of the actual roles and status of older people in American society.

The Role Areas of the Elders in Our Society

The lives of older people can conveniently be seen as consisting of role-playing in a number of role-areas. These role-areas have been defined by Albrecht (1) on the basis of observation of the old people in a midwestern city as follows: parent, grandparent or great-grandparent, home member or homemaker, member of extended family or kinship group, church member, social or business club member, member of age-group of the elders, participant in informal social groups, citizen, worker or money-earner and user of leisure time.

Within each role-area a number of specific roles can be identified. They range from inactivity or non-participation to extremely active role-playing. These specific roles are defined in the following pages and the proportion of people over 65 fitting each role is given. These figures were obtained from a study of a cross-sectional sample of 100 people over 65 in a midwestern county seat of 7,000 population (2). No doubt the actual proportions would vary somewhat in communities of other sizes and other parts of the country but no new roles are likely to be encountered. The people in the sample did not represent some 10 per cent of the old people who were so ill or so feeble that they could not be interviewed. While a few very feeble or sick people were seen, this group is not adequately represented in the sample. Consequently, the proportions of people in these passive and non-participating roles are slightly underestimated in these findings. The numbers in parentheses in the following description represent the "social approval value" of the role, which was determined in a way that is described later in this chapter.

A. Parent

In the sample, 78 per cent had living children. Their roles were as follows:

1. No relations with children, no interest in them, seldom or never hears from them, may reject them or be too ill to care; 4 per cent (all men) (1).
2. Dependent on children entirely or partially for care and support; 6 per cent (mostly women) (2).
3. Shares house with children, mutual help and mutual dependence; 8 per cent (mostly women) (2).
4. Full or partial responsibility for children; 7 per cent (2).
5. Mutual independence but close social and affectional relations between parent and children; 75 per cent (4).

B Grandparent or Great-grandparent

Seventy per cent of the sample had grandchildren, and 23 per cent had great-grandchildren. Their roles were:

1. No relations with grandchildren or great-grandchildren, no interest, may reject them; 4 per cent (mostly men) (1).
2. Some communication about descendants but no direct contact; none of the grandparents, 30 per cent of the great-grandparents (2).
3. Sees and hears from descendants occasionally, social participation may be active, but no responsibility for them; 72 per cent (4).
4. Occasional or part-time responsibility for descendants; 24 per cent (3)
5. Full responsibility for care of grandchildren or great-grandchildren; none (2).

C. Home Member or Home Maker

1. No responsibility, cared for by others; 16 per cent (people who were ill, lived in a home for the aged, or in a boarding-house) (3).
2. Helps others in the house but dependent on them; 5 per cent (2).
3. Shares responsibility for home, usually with spouse; 62 per cent (4).
4. Fully responsible for home with little or no help from others; 17 per cent (3).

D. Member of Extended Family or Kinship Group

1. No living relatives or no contact with and no interest in relatives; 13 per cent (1).
2. Correspondence with kinfolk but little or no direct contact; 21 per cent (3).
3. Occasional visits with kinfolk, at family reunions, holidays, on trips, etc.; 30 per cent (3).
4. Frequent visits and communication with kinfolk, close family feeling; 36 per cent (4).

E. Church Member

1. Rejects religion and church; 4 per cent (1).
2. No church attendance, no affiliation; 24 per cent (1).
3. Passive interest, seldom attends church, may listen to sermons on radio; 15 per cent (2).
4. Frequent and active participation but no responsibility; 55 per cent (3).
5. Active participation, with responsibility as church officer, committee member, etc.; 2 per cent (4).

F. Social or Occupational Club Member

While all people are theoretically eligible for social organization membership only the men and a few working women are eligible for business club membership, making up 48 per cent of the sample

1. No membership, no interest For social clubs [illegible] per cent, for business clubs 75 per cent of those eligible (1)
2. Passive interest, reads about them, may be nominal member For social clubs 14 per cent; for business clubs, 2 per cent (2)
3. Frequent and active participation but no responsibility For social clubs 20 per cent; for business clubs, 23 per cent of those eligible (3)
4. Active participation, with responsibility as officer or committee member (4) for social clubs, 8 per cent; for business clubs none (4)

G. Age-Group Member

As a member of the age-group of the elders of society, the individual has opportunity to associate with many or with few friends, to keep up associations through visits, telephone, mail and membership in old people's organizations

1. *No interest in age-mates and former friends*, none (1)
2. *Associates with age-mates infrequently, very seldom visits or receives visits* from old friends; 10 per cent (2)
3. Occasional visits from and to age mates, communicates with few old friends by card, etc.; 37 per cent (3)
4. Active social relations with age mates locally and in nearby places, by visits, telephone, mail, 49 per cent (4)
5. Active social relations with age mates locally and in distant places, visits and receives visits for extended periods, participates actively in associations of older people; 4 per cent (4)

H. Participant in Informal Social Groups

Outside of the close family and kinship group, informal social and clique relations may be carried on in the community and in the wider society with people of all ages

1. No participation, solitary, associates with no one in a social way, 4 per cent (1).
2. Scattered social contacts in non-intimate groups, such as tavern or cigar store or weekly church services, 71 per cent (2)
3. Loosely-knit relations with people in their home or in own home, 18 per cent (4)
4. Close-knit relations in social cliques, either of own sex or with spouse in couples; 7 per cent (4)

I. Citizen

1. No interest in civic or community affairs, no participation; 23 per cent (1).
2. Routine interest, shown mainly by fairly regular voting in elections; 62 per cent (4).
3. Active participation, works for political and community projects, but takes no responsibility, 12 per cent (3)
4. Carries civic responsibility, holds elective office or is officer of community civic organization, such as library board, school board, Red Cross; 3 per cent (3)

J. Worker or Money-Earner

Fifty-three per cent of the sample were gainfully occupied or had been prior to retirement. This included all men and 14 per cent of the women. The percentages refer to this group.

1. Not working, no pension from occupation, most receive Old Age Assistance; 17 per cent (3).
2. Does odd jobs occasionally; 9 per cent (all men) (3).
3. Working at a job of lower prestige than formerly; 4 per cent (2).
4. Retired and living on a pension from former employment (including Social Security); 9 per cent (4).
5. Retired, but managing own property and living on income from it; 13 per cent (4).
6. Working part-time at former occupation; 6 per cent (4).
7. Working full-time but responsibility diminished from that of peak of career; 14 per cent (3).
8. Working at the peak or plateau of career, no diminution of responsibility or activity; 28 per cent (2).

K. User of Leisure Time

1. Vegetates, just sits around except when doing necessary work; 7 per cent (1).
2. Has passive recreations, listens to radio, watches television, reads, goes to movies occasionally, sits and watches the world go by with some interest; 30 per cent (3).
3. Has some active recreations which he carries on individually or with others; still has time on his hands, however; plays indoor games, plays outdoor games—shuffleboard, bowling, croquet, golf; writes letters, reads widely, crochets, knits, quilts; gardens, does wood or metal work, crossword puzzles, works on collections; 61 per cent (4).
4. Has a variety of recreational interests and activities which keep him busy, takes initiative in planning recreation, writes articles, gives talks, known as a person with well-developed special interests, has gained prestige thereby; 2 per cent (4).

Social Approval Values of the Various Roles

Each of the roles that have been described has a value or status in the eyes of the people. If we knew what the average status-value of each role is, we could add together these values for all the roles filled by a particular person and thus get a social approval score for his particular collection of roles. Consequently, we have sought to find out from the American public just how it rates the various roles that older people may play.

To accomplish this, we drew up a questionnaire listing 96 activities which older people might engage in. Examples are:

Reads political news and votes regularly.

Plays games with a group of friends regularly.

Has nothing to do with church.

Goes to live in an Old People's Home.

Shares home with a married son or daughter and retains ownership of the home.

Holds onto his job as long as he can, even though other people think he is too old for it.

Retires from work between the ages of 65 and 70.

The respondent to the questionnaire was given the following directions: Below is a list of things that people over 65 might do. Some of these things are very good things for older people to do, and some are not so good. Please tell how you feel about older people doing these things by checking the columns that agree with your attitudes. Sometimes a thing will be good for a man to do but not for a woman. So please check once for men and once for women. If something does not apply to both sexes, check only the column for the appropriate sex. Assume that the old person is in reasonably good health, unless the item says that he is not.

Respondents were asked to register approval or disapproval as follows:

A. This is all right, I approve of it.
B. Neither good nor bad.
C. This is a bad or foolish thing to do.

The questionnaires have been filled out by approximately 100 men and women in each decade of life from 20 to 60 and by a smaller number in the age-periods, 60 to 65, 65 to 69 and 70+. The people responding to the questionnaire have been mainly middle-class people.

The social approval value of each activity can be determined by giving scores of 0, 1 and 2, respectively, to the answers, "Bad or foolish thing to do," "Not good, not bad," and "A good thing to do, I approve of it," and by averaging the scores from the people who filled out the questionnaire. This has been done, with the result that each of the 96 activities has a "social approval value". These values show little variation with age of respondents from 20 to 64, but there is some shifting in values of certain activities in the eyes of people over 65. Since it is the age-group 20 to 64 that pretty well represents public opinion, we have used the values derived from this group.

For most of the roles described previously, there is one or more of the [illegible] questionnaire to which a given role may

of the activity or activities that correspond most closely to it. This has been done after grouping the scores for the 96 activities into four levels of approval. These levels are scored from 1 to 4 and the various roles are given scores from 1 to 4 accordingly. These scores are given in parentheses following each of the role-descriptions in the preceding list.

Thus we have a rough approximation to the social approval value of each of the roles an old person may play and we can add these scores to get a social approval score for each person whom we study.

When this is done, it becomes possible to study the relation of a person's social approval score to his personal adjustment and to other of his characteristics.

Personal Adjustment and Social Approval

No doubt a person's happiness and personal adjustment depends a great deal on his conception of the attitudes of others towards him. Hence a person who plays roles that are generally approved will tend to be happy and well adjusted. This hypothesis was tested in the community study by comparing the score for personal adjustment (from the attitude inventory of *Your Attitudes and Activities* by Cavan, Burgess, Havighurst and Goldhamer (3) with the social approval score. The coefficient of correlation of the two sets of scores was .60.

Still another way of measuring personal adjustment is to secure ratings from people who know the individual in question and who are able to interpret behavior objectively. Such a rating was obtained with the aid of the Cavan Adjustment Scale (3) which was filled out by three psychologists for each person in the study. The coefficient of correlation of social approval scores with scores on the adjustment scale was .76.

Thus it is clear that, in a general way, the personal adjustment of an individual is good when his roles have high social approval value. However, there are a few exceptions to the rule. The exceptional cases consist of small groups: 1) Widows and married women with close and affectionate family relations but little or no social or civic participation outside of the family. Often these women are very happy and well-adjusted, although their roles outside of the family and sometimes the church are inactive and poorly valued by the community at large. 2) Single men, usually of lower socio-economic status, who have very few socially approved roles, but have a small group of cronies with whom they "hang out" in a tavern, or have other recreations which make them reasonably happy. These men do not care about disapproval from middle-class attitudes of the community as long as they are physically comfortable and can do pretty much what they please. 3) A few pre-senile people, who have euphoric attitudes about themselves although they fill inactive or socially disapproved roles.

Ageing and Role-Activity

Degrees of activity in each role-area have been described by Albrecht and rated on a ten-point scale. Thus the mean role-activity of a person

may be determined by rating his activity in each role area and taking the average of the ratings. Albrecht has found a mean activity rating of people over 65 of the order of 4.4. This is decidedly less than the ratings of middle-aged people which average about 6 on the same scale (only 2 per cent of the older people received an average mean as high as 7).

Among the people over 65 in the midwestern community where this study was made, women exceeded men slightly but reliably in mean role-activity. There was a decrease of role-activity with age, although not a very large decrease. (Coefficient of correlation of role-activity with age was −.22.) There was also an increase of role-activity with increasing socio-economic status. (Coefficient of correlation of role-activity with a socio-economic index was .47.) With respect to marital status, those men and women who were married and living with their spouses had the highest role-activity scores. This undoubtedly reflects the greater opportunity for informal and formal social activity on the part of married men and women, as well as a tendency for widowed people to withdraw from social activity.

Groups who rise in status as they reach old age

Contrary to the trend of reduction in role-activity, in social approval score and in status as people grow older in American society, there are a few small groups whose members seem to rise in status. Two such groups appeared in the midwestern community study.

One group are the upper-class widows. These women, if they lose their husbands when the latter are in their sixties, which often happens, are themselves in their early sixties or late fifties when they are widowed. Now, in addition to their own roles as upper-class women, they take over some of the roles of their deceased husbands. Frequently, they retain an interest in their husband's business or they keep active control of his property and, consequently, they take on a highly respected and powerful business role. They sometimes take the leadership of the family and exercise the status of the deceased grandfather in giving property to children and grandchildren, in helping to decide about marriages of grandchildren, etc.

Another group who gain status are the retired farm-owners. In the part of the midwest where the study was made, an ordinary farm will support two families; thus, the owner can retire and rent his farm to a younger man and live comfortably on the income. Consequently, a number of farm-owners move into town, buy a house in a good neighborhood, drive a first-rate automobile, and go to Florida or Arizona for the winter. These men would hardly be classed above lower-middle in social status while they are still working their farms and often paying on mortgages.

their later years they may acquire some of the symbols of upper-middle-class status.

The Possibility of General Change in Roles and Status of Older People

Status and roles change very slowly in a society that is stable. Even in such a changing society as we see in modern America, we cannot expect the roles and status of older people to change very much in as short a time as one generation. However, changes do occur, under the impact of economic and social forces and as a result of deliberate attempts to make changes. An example of changing status due to economic change is seen in the case of the elderly farmer. In the late 1920's and early 1930's farm incomes were so low that few farm-owners could afford to retire and live on incomes from renting their farms. But as farm incomes rose, this group increased substantially in economic status and, consequently, in social status.

If any large group of Americans were to seek deliberately to increase the status and improve the roles available to older people, they should probably direct their efforts along the following lines.

1) Provide more active roles in social organizations for older people. As the data reported earlier in this chapter show, most older people are relatively inactive in social clubs. But there is some question whether younger and middle-aged adults will make the necessary adjustments to give older people more participation in such organizations of mixed ages. Consequently it might be desirable to:

2) Provide more active roles in organizations for the age-group of the elders by encouraging the development of old people's organizations. This would meet with general approval by middle-aged and younger adults, although a good many older people dislike to be thrown with people their own age for any large part of their time.

3) Provide more active roles in church life for older people. This seems to be an excellent possibility. Churches may organize activities primarily for older people and they may at the same time reach out and bring older people into their activities for mixed age-grades.

4) Provide for a slow tapering-off of work for men and for employed women. Instead of retiring men and women completely from employment at an arbitrary age, such as 65, assignments may be made to permit older people to carry on with part-time work or with work of less responsibility.

It is probable that changes of the kinds just described in the roles of older people would lead to improvement in the status of older people and to making them happier and better adjusted.

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PERSONAL ADJUSTMENT IN OLD AGE

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The study of personal adjustment and maladjustment in old age has both theoretical and practical significance. Certain maladjustive types of behavior tend to increase in frequency in old age. By a study of the processes by which maladjustments occur and of the factors associated with them, new light may be shed on personality integration and disintegration. From the practical side, large numbers of maladjusted old people are a burden upon society—and a burden likely to increase with the increasing proportion of old people in our society. Any indication of the causes of maladjustment and suggestions of ways to prevent or decelerate the process are of great importance both in preserving the happiness of old people and in relieving the social burden.

Indices of Crucial Maladjustment in Old Age

First admission rates to state mental hospitals for psychotic patients climb rapidly from age 15 to the age period 35 to 39, level off into a plateau until age 55 to 59, after which a spectacular increase occurs. A more detailed analysis, however, shows that not all types of psychoses fall into this pattern. All forms of psychoses except psychosis with cerebral arteriosclerosis and senile psychosis reach a peak rate somewhere between the ages of 30 and 55, then decline. The two psychoses of the senium begin at about age 40, continue at a steady rate until age 60, after which the rate increases with rapidity until age 70 and over. Unfortunately, the official report does not segregate age periods after age 70. Table 1 shows the rates for non-senile psychoses and for the mental diseases of the senium by age periods. Although some disagreement exists among authorities regarding the extent to which organic changes in the brain are responsible for senility,

some authorities regard the stresses of experience as a factor in the development of many cases of senility (6, 14).

Suicide, the last refuge of those who have lost their zest for living, also has a high rate for the older age periods. Although the suicide rate does not increase throughout old age, the high rate that has been reached by

TABLE 1

Rate of first admissions to state mental hospitals in the United States and incidence of suicide in Chicago by age, per 100,000

Age	All psychoses except of the senium, 1948*	Psychoses of the senium, 1948*	Suicide, 1929–1935†	
			Male	Female
Under 15	0.7		0.52	0.42
15–19	22.8		1.43	2.04
20–24	37.6		7.28	5.03
25–29	45.1		12.01	7.16
30–34	54.2		14.29	6.90
35–39	60.0		19.10	7.02
40–44	62.2	0.7		
45–49	63.1	2.1	39.49	7.89
50–54	59.9	5.9		
55–59	53.9	15.4	58.36	9.86
60–64	44.0	45.9		
65–69	24.2	97.9	71.36‡	12.02‡
70 and over	16.2	257.1	72.90§	9.15§

* Based on Mental Health Statistics, Current Reports Federal Security Agency, Public Health Service, National Institute of Mental Health, Series MH-B50, No 4, 8, June 1950

† Mowrer, E. R. Disorganization, Personal and Social, p. 622 Lippincott, Philadelphia, 1942

‡ Age 65–74

§ Age 75 and over

the beginning of the old age period is maintained without diminution for males and only slightly decreased for females, as table 1 shows.

Criminal behavior as a whole occurs with higher rates during young adulthood than at any other period. Nevertheless, certain types of criminal behavior are more characteristic of the old than the young. Vagrancy, chronic drunkenness, sex crimes other than rape (exhibitionism, molestation of children, and so forth) and emotional murders tend to be more characteristic of middle-aged and older men than of young men, whereas crimes of daring and violence belong to the young and those involving business acumen to the middle-aged (11, 15).

Psychotic, suicidal and criminal people are easily identifiable because

of their markedly divergent behavior. The relative frequency of these types of behavior in old age suggests that among "normal" old people milder forms of maladjustment may exist, and indeed may be the forerunners of more severe mental and behavior disorders.

Study of Personal Adjustment in Old Age

Personal adjustment defined

Personal adjustment is the process by which the individual seeks to satisfy his innate and acquired needs and drives in the physical and cultural environment in which he finds himself. In a stable society, with few changes from generation to generation in technical means of manipulating the physical environment and few changes in philosophy and social relationships, the processes of personal adjustment tend to become routinized. Over a long period of time the culture becomes adjusted to man's needs, and man's early training tends to fit him into the cultural controls and restrictions. Men may be taught to restrict certain drives and to curb spontaneous impulses. In compensation, they receive the approval of their fellow men. The culture, through previous trial and error situations, has discovered sufficient controls to give an orderly society, combined with sufficient outlets and satisfactions to prevent great restlessness or rebellion. In such a society, it could be said that most people are well adjusted personally.

A general definition of good personal adjustment may therefore be made: the well-adjusted person is the one who is able to satisfy his needs quickly and adequately within the controls and outlets provided by his culture. The needs as defined by the culture and the controls and outlets may differ from one society to another; therefore, in any given society specific study alone would reveal what needs were recognized, in what terms they were formulated, how they were controlled and what means of satisfaction were provided.

Each person as he grows from infancy to adulthood comes to define his needs in specific fashion and to desire specific types of satisfaction. The older person is not simply hungry, but craves certain foods. He does not want to be loved in general, but to receive the love of specific persons. He wants to sleep on a mattress of a certain degree of hardness or softness. He wants his recreation to take the form of music, sports or reading, as the case may be. The adult also has accepted the regulative demands of society. He keeps his more intimate love relationships within the family; he meets the expectations that he will work at a gainful occupation (or in the case of a woman manage a home and rear children); he joins various of the organized groups available in his community and conforms to their rules. In other words, he has a fairly well integrated and predictable per-

sonality. He knows what is expected of him, what he conceives as his needs, and how he plans to satisfy them. He is satisfied when his plans are successful and dissatisfied or acutely unhappy when he is thwarted or denied success.

From a behavior standpoint, we may think of these culturally developed types of behavior as roles. Each society provides a number of roles through which people express and satisfy their needs. Although some roles tend to remain fixed throughout life, others change (see Chapter 39). In fact, from time to time throughout the life cycle, changes in roles are expected by the culture and pressure is placed upon individuals to adapt their attitudes and habits to the change. Other changes are precipitated by physical growth, illness or accident. Many role-changes occur during old age. Some of these are social in origin, as the establishment of "legal old age" at 65 and the widespread use of this age for automatic retirement, whereby the role of wage-earner is exchanged overnight for the role of the permanently unemployed. Others result from chronic disease; heart disease, for instance, may create the chronic invalid. Still others come from deaths; the widow results from death of the husband and the "last leaf" from the deaths of all of one's generation of relatives and friends. Impoverishment due to loss of employment creates the old age pensioner. Other changes in role are less tangible but none the less real in their effect upon personal adjustment. The widespread attitude that vitality, privilege and authority belong to young and middle-aged adults erects a barrier between these attributes and the old, expressed in the easing of old people out of places of prestige and authority. Examples are the speech of appreciation and gift to the club president who has served his allotted time and has reached old age, coupled with the expectation that he will not seek reelection; the shifting of the active industrial president to a passive position on the board of directors; and the protective attitude of the young towards the able-bodied old. The old person may find it difficult to accept the new roles and may feel that his needs are not met by the new roles of old age.

Personal adjustment and social organization

The ability to adjust is related to the social organization of society. Social organization refers to the process of coordination between different functions of society, that is, between institutions, folkways and mores. A *well-organized society* has a high degree of coordination among its functioning parts. All important needs are controlled and modified through institutions or less formal modes of behavior and group life. In a stable society, a high degree of coordination develops over the years. In a changing society, with many innovations through inventions and diffusion from other cultures, coordination tends to be replaced by conflicts among institutions

and ideas, overlapping of functions and sometimes failure of the society to provide for some needs. In the United States, for example, hand crafts have been replaced by machinery that requires a quick young hand to operate. The change has occurred more rapidly than means have been developed for retraining old people or of finding new types of work for them. The older worker, therefore, often is stranded.

Maladjustment

Many of the enforced changes in roles and in the social organization are unwelcome to the old person. They alter the means that he has long used to satisfy his drives and needs; his customary processes of quickly and adequately satisfying his needs are disturbed or destroyed. A period of maladjustment then follows. Under these circumstances, he may revert to individual impulses and disregard the cultural patterns (as the old vagrant who begs money or food); he may seek escape through the use of drugs or alcohol, by running away or committing suicide; he may attempt to repress his dissatisfactions only to find himself involved in neurotic anxieties or compulsions; or he may actually withdraw from reality into a system of delusions. The majority of people experience less severe reactions, such as restlessness, dissatisfaction with social relationships or minor anxieties and emotional disturbance. Most old people manage to reorganize their lives either by redefining their needs or by finding satisfactions through new roles and activities.

Study of personal adjustment in old age

One way in which personal adjustment can be studied is through learning the attitudes of people towards their experiences. Attitudes that express happiness and contentment indicate good adjustment; those that reveal bitterness, fear, despair or other destructive feelings and emotions are associated with poor adjustment. In a study begun in 1944 under the guidance of the Subcommittee on Social Adjustment in Old Age of the Social Science Research Council, an attitude inventory was developed to measure the attitudes of old people towards the dominant situations and conditions of their lives. The categories included in the inventory were health, family relationships, friendships, leisure-time activities, clubs and organizations, employment, economic security, religion, feeling of usefulness and happiness. To accompany the inventory, a schedule was constructed asking for factual information on many of the areas listed above as well as upon situations relating to earlier periods of life. Details on construction of the inventory, reliability and validity will be found in reference (1); the complete inventory and the schedule of social data used in connection with it are also printed in the above reference; for further confirma-

tion of reliability and validity, based on a carefully selected sample of 100 people from a small community, see reference (4). Through interviews and mail service, attitude inventories and schedules were secured from 2,988 men and women widely distributed in territory, occupation, and social status and covering the age range of 60 to 100 years. The inclusion of selected lists of retired Methodist ministers, widows of ministers, retired public school teachers and the alumni of one college and one university, weights the total group with certain professions and a higher educational level than the average. The inventory and schedule could not be filled out by senile persons; therefore the group represents normal older persons.

The attitude inventory consisted of statements of attitudes ranging from very unfavorable to very favorable towards the ten areas listed in the preceding paragraph. In each area or category the least favorable attitude received a weight of 1, and the most favorable a weight of 7, with intermediate attitudes receiving the intervening weights. The average of the weights checked for any one category gave the score for that category and the addition of these partial scores yielded a total attitude score indicative of adjustment or non-adjustment. The categories are repeated below, with the most favorable and the least favorable attitude in each category.

Most favorable attitude (weight of 7)	*Least favorable attitude (weight of 1)*
Health	
I never felt better in my life	If I can't feel better soon, I would just as soon die
Family	
I get more love and affection now than I ever did before	I never want to see my family again
Friends	
My many friends make my life happy and cheerful	I never dreamed that I could be as lonely as I am now
Leisure-time	
As the years go by, I seem to get more and more pleasure out of life	The days seem endless
Organizations	
One of my greatest joys is club work (lodge, union, etc)	Organizations no longer mean anything to me
Work	
I do better work now than ever before	I can no longer do any kind of useful work

and ideas, overlapping of functions and sometimes failure of the society to provide for some needs. In the United States, for example, hand crafts have been replaced by machinery that requires a quick young hand to operate. The change has occurred more rapidly than means have been developed for retraining old people or of finding new types of work for them. The older worker, therefore, often is stranded.

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Although the majority of both men and women rated their health as good or very good, approximately one-third of each sex rated their health as fair, and 7 per cent of the men and 8 per cent of the women considered their health as poor or very poor. A third of the men had none of a list of common physical defects of the old and a third had one defect only; 21 per cent had two, 8 per cent three, and 5 per cent four or more, the highest number of defects checked by one person being seven. The women had much the same distribution, with a few more checking four or more difficulties. The six most frequently mentioned physical difficulties were, in order: crippled condition of the limbs, partial or complete deafness, poor eyesight or blindness, high blood pressure, heart trouble and stomach trouble. It is significant that all these, with the possible exception of the last, interfere with normal activities or reduce communication with other people; in other words, their effect is to deprive the person of accustomed contacts and to isolate him physically or socially. Also, they tend to be chronic and to eliminate any hope for future restoration to normal physical capacity. Such conditions are important, therefore, in personal adjustment, for they prevent satisfaction of needs and interests; if the old person is unable to compensate in some way he must either resign himself to limited contacts or become restless, dissatisfied, unhappy. The third criterion of health referred to bedfastness involving pain and care by another person Again, most of our subjects had had little difficulty, but a minority were bedridden, suffered and required care. A word of caution should be given against accepting the percentage distributions as showing the amount of ill health or number of defects in the general population; obviously among those who received the schedules by mail, the more seriously handicapped could not respond.

In view of the isolating and immobilizing character of the physical handicaps suffered by old people it is not surprising to find a relatively high correlation between the conditions reported by the old and their attitudes. The health rating, freedom from physical defects and illness rating have coefficients of correlation of .51, .35 and .36, respectively, with the health attitudes for men, and of .40, .34 and .42 for women. The coefficients showing correlations of the same three measures of health with the total attitude inventory are, for the men, .45, .36 and .31; and for the women, .45, .36 and .36. Physical condition, therefore, assumes importance as a factor in personal adjustment.

Family and friends

The family attitude scores are related to the marital status of both men and women. The divorced and unmarried had the least favorable attitudes towards family life. These two categories represent only a small percentage

of old people; for practical purposes the contrast is between those married and living with the spouse and the widowed. Among the men, 50 per cent of the married but only 31 per cent of the widowers had highly favorable attitudes towards family life; among the women the contrast is less marked, the percentage with the favorable attitudes being 48 and 42 respectively.

The effect of widowhood on the old person's outlook on life assumes more significance when we inquire into the proportion who become widowed as the years advance. According to the Sixteenth Census for 1940 (the figures have been reanalyzed by age periods), 11 per cent of males at age 60 to 64 were widowers; the percentage increases rapidly with age until at age 85 and over, 59 per cent are widowers. For women the percentages are more appalling: 31 per cent are widows at age 60 to 64 and by age 85 and over, 85 per cent have lost their husbands by death. For women over 70 and men over 85 years of age, death of mate is the expected experience rather than the exception.

Since there are relatively few remarriages in the later years, possible compensations in the way of alternative affectional relationships are important for personal adjustment. Old people with neither children nor close relatives, although few in number, had less favorable family attitudes than those with close familial ties. Too much emphasis should not be placed on the existence of children, however, as close relatives seemed to create as favorable a situation as children. At the age that our subjects had reached, the children frequently were middle-aged adults who perhaps had been separated from their parents for the length of a generation. Value seems to lie in the existence of some close family tie more than in the degree of relationship.

Friends as well as family members may create warmth of contact and the feeling of intimacy that most people are accustomed to and crave. Favorable attitudes towards friends were found to be related to the number of close friends (r of .23 for men and .25 for women) and frequency of seeing friends (r of .15 and .19). Friendships with children and young people also were related to favorable friendship attitudes. These same measures of friendship also all had positive but low correlations with the total attitude score (r ranges from .14 to .27). These coefficients are considerably lower than the coefficients showing the association of health measures with the total attitude score.

Leisure-time activities

Prior to old age and retirement, both men and women are accustomed to having their time well filled with familiar work that gives organization to their days. Leisure is secondary, although it also fills specified hours—evenings, Saturdays, Sundays, holidays and vacations. Except for vaca-

tions, however, the average adult does not have a succession of idle days. The old person who has retired is faced with a seemingly endless succession of days of leisure. Half of the men and more than half of the women stated that they had all day free; among the older age groups the proportion with complete freedom of time greatly increased. The men with all day at their disposal had less favorable attitudes toward leisure than any other category; the best attitudes were found among those with only a few hours of free time per day. Women liked leisure in even smaller doses and had the most favorable attitude when they had almost no free time.

The radio is often regarded as a great boon to the old. Nevertheless, those who listened to the radio only from a few minutes to a few hours per day had more favorable leisure-time attitudes than those who spent the entire day at the radio. Those who never or almost never listened to the radio also had poor leisure-time attitudes. This group includes those without radios and also the deaf. The radio therefore is only a partial answer to the problem of a happy leisure.

Hobbies, often advocated for the retired person, are closely related to the way in which the old person regards his leisure time. Among men with four or more hobbies, 76 per cent had very favorable attitudes toward leisure; the percentage decreased regularly until it dropped to 39 per cent with good leisure-time attitudes among those with no hobbies Among women the corresponding percentage for those with many and no hobbies were 51 and 37. But hobbies apparently are not something one starts in old age. Among 1,054 hobbies listed by men, 45 per cent had their beginning before the age of 20, 30 per cent between ages 20 and 40 and 15 per cent between 40 and 60 years; only 10 per cent were started after the age of 60. The percentage distribution for women is very similar.

The most popular hobbies listed by men were gardening or farming, outdoor individual sports, reading, organized sports and shop work; by women, reading, sewing and making quilts, gardening, cards and other table games and music. With the exception of gardening among the men and reading and sewing among the women, these hobbies all decreased in popularity as age became greater; or, men and women in their sixties, who often are still employed, had more hobbies than those in their seventies and eighties, who had more leisure.

Attendance at clubs, lodges, church groups and other organized groups is another means of occupying leisure time. As might be expected, attitudes towards organizational contacts varied with the number of organizations and the regularity of attendance. Holding of office also created favorable attitudes towards organizations. But organizational contacts have some of the same characteristics as hobbies. Old people do not tend to join new organizations. The most popular age period for joining was 30 to 40 years

of age for men and 30 to 55 years for women. Moreover, withdrawal from clubs, irregular attendance and failure to hold office all increased with age.

Leisure-time activities are related not only to the attitudes towards leisure and organizations but also the total attitude inventory score. Number of organizations, frequency of attendance, and number of offices held have coefficients of correlation of .26 to .30 with the total attitude inventory score. Number of leisure-time activities correlates .21 for men and .26 for women, while a total score on all types of group participation has a coefficient of .43 for men and .39 for women with the total attitude inventory score. These coefficients place group participation as a significant item in the personal adjustment of old people; unfortunately, it is a type of experience that old people find difficult to initiate in old age and that declines as age increases.

Work

The loss of employment or involuntary retirement seems in many ways the greatest trial of old age for most men; women do not face the same problem, aside from the small group who have followed a lifetime career of paid employment. Whereas men secure their primary status and feeling of worth from their jobs, most women receive it from their roles as wife, homemaker and mother. The active role of mother usually has disappeared and been adjusted to during middle age; widowhood often destroys the role of wife; the role of homemaker continues, however, and usually is capable of adjustment to lessened strength and slowing of movements so that many women never experience the complete and sudden cessation of work that overtakes many men between the ages of 65 and 70. The magnitude of the problem is evident from figures in the Sixteenth Census for 1940 (figures have been reanalyzed by age periods) as shown in table 2.

Analysis of work retirement is not simple. The man may feel a loss of personal status; unwanted leisure is almost certainly a problem; and decreased income may threaten security and perhaps necessitate acceptance of aid from children or application for Old Age Assistance or some other form of relief. For others, however, retirement may be a release from uninteresting work or great physical or mental strain. The data from our study indicate that those who welcome retirement are less well adjusted than those who regret the loss of regular employment.

More than two-thirds of the men who were continuing in their usual work felt well satisfied with their work; a few even believed that they were doing better work than ever before. Among those without paid employment, only one-third thought that their substitute activities gave satisfaction. Those who believed they could no longer do any kind of useful work varied from 9 per cent among those still employed at their usual jobs

to 40 per cent for the unemployed. Among housewives, 23 per cent of those still engaged in homemaking considered they did not do useful work; the percentage doubled, however, among those no longer doing housework. The latter group includes not only the physically handicapped (two-thirds of whom thought they could no longer do useful work), but also those without opportunity for housework because they lived with children or in institutional homes. Although the feeling of uselessness may be realistic in that the person is actually unable to work, nevertheless it shows an acceptance by the person of a lowered social role that may be linked with a general feeling of unworthiness.

Several questions were asked regarding economic security. Four-fifths of both men and women stated that they considered that their present sources of income gave permanent security, in response to a direct question, and approximately two-thirds made scores indicating feelings of security

TABLE 2

Percentage of men over age 60 who are unemployed, for the United States in 1940, by age periods

Age	Percentage of men unemployed
60–64	29
65–69	46
70–74	64
75 and over	83

on the attitudes scale on security. The most secure were those whose incomes were derived from savings or investments or from several sources; least secure were those receiving Old Age Assistance with 53 per cent of the men and 46 per cent of the women receiving such Assistance feeling definitely insecure. Those dependent upon earnings, children or institutional homes fell into intermediate positions. Employment, therefore, is related more closely to feelings of usefulness and capacity to work than to feelings of economic security.

The various measures of employment and work-satisfaction also had a low but positive correlation with the total attitude inventory score.

With retirement comes a decrease in income with necessary adjustments to reduced expenses. The old person or old family may find it necessary to move to a smaller home in a less desirable part of the city, to reduce luxuries and even comforts and to give up certain recreations or hobbies. From such items a rating was secured on downward socio-economic mobility. This rating has a negative correlation coefficient of −.25 for men and −.27 for women with the total attitude inventory; that is, the greater the degree of downward mobility, the lower the attitude score tends to be, showing an

association between downward mobility and unfavorable attitudes. The rating on present economic status, as judged by the old people, without regard to change of status, has a coefficient of .30 for men and .31 for women with the total attitude inventory score.

Loss of employment and its correlates of loss of socio-economic status and uncertain sources of income therefore are associated with feelings of work-incapacity, uselessness and insecurity and with a low adjustment score.

Religious activities

Religion and church affiliation may be regarded in several ways—as providing group activities that are perhaps of increasing importance as the family breaks apart through death; as giving philosophical compensation and acceptance of handicaps through resignation; and as providing a hope for the future through a belief in immortality.

Fifty-four per cent of the men and 61 per cent of the women considered that religion was a great comfort to them. Since ministers and widows of ministers are included, these percentages may seem higher than would be expected for a less selective group. The ministerial groups and also retired teachers were therefore omitted and calculations made for a miscellaneous occupational group, which revealed that 42 per cent of the men and 60 per cent of the women believed that religion was a great comfort to them. The feeling of comfort in religion was closely related to frequency of church attendance, regularity of listening to radio sermons, frequency of Bible reading and belief in an after-life.

As age increases favorable religious attitudes also increase. Whereas 38 per cent of the miscellaneous group of men believed that religion was a great comfort to them in the early sixties, more than 50 per cent of those in their eighties had this attitude. Among women the favorable attitudes increased from 51 per cent for women in the early sixties to 69 per cent for those over 85 years of age. Church attendance dropped with age, but frequency of listening to radio sermons and reading the Bible increased. Religion definitely is of importance to the present generation of old people.

Religious activities also are related to the total attitude score. Frequency of attendance at religious services has a correlation coefficient of .41 with the total attitude score for men and of .36 for women. These coefficients are for the entire group, including ministers, widows of ministers and teachers.

Satisfaction with the present

The foregoing discussion has focused attention on some changes that come with age that make it necessary for old people to change their mode

of living. In each area of activity we have shown the relation to attitudes that have developed in response to concrete and tangible situations. In the attempt to reach a more generalized reaction to life, the attitude inventory was constructed to include the category of happiness which shows contentment or satisfaction with the present. Forty-three per cent of the men and 58 per cent of the women checked attitudes that indicated they were as happy as when they were younger. Forty-seven per cent of the men but only 29 per cent of the women thought that their lives were *brimming over with happiness—they were enjoying the best years of* their lives; they were so happy they almost wished life could continue indefinitely. But small proportions—10 per cent of the men and 13 per cent of the women—considered that their lives were filled with worry and that they had less and less for which to live.

Another question, "What was the happiest period of your life," also brought interesting responses. The most frequent response, given by 53 per cent of the men and 42 per cent of the women, was that all periods were equally happy. The next most frequent response, accounting for 22 per cent of the men and 30 per cent of the women, placed the happiest period during ages 20 to 40 years, often with the added remark "when the children were all home and growing up." The years below 20 and the period 40 to 60 years of age each received between 8 and 13 per cent of the responses. Only 6 per cent of either men or women placed the happiest period after 60 years of age, although, as noted above, a large percentage did not think there had been any diminution of happiness with old age. When a definite period was distinguished, it tended to be young adulthood, the period when men were establishing themselves in business and women were most completely functioning as wives and mothers.

The periods of greatest happiness show some relationship to the scores on the category of happiness attitudes. The highest scores were made by men and women who felt continued happiness or were happier after age 60 than at any other time; lower scores were made by those whose happiest period had been prior to age 60; and the lowest scores of all were made by those who believed that their happiest period had been during childhood.

These findings suggest that, while the period of old age is not outstanding as the happiest period of life, nonetheless it is a time of contentment to most people. Those who look furthest into the past to find their happiest period tend to be the ones least happy with their present lives.

When these and other indices of happiness are related to increases in age, some evidence appears of greater contentment and less tendency to discriminate between age periods as age advances. For example, twice as many men (62 per cent) in their eighties thought that all periods of life were equally happy as did men in their sixties (32 per cent). This trend

is not shown by women. The percentage of men selecting young adulthood as the happiest period decreased irregularly with age. There was also more of a tendency for those 75 years old or over to regard the present period of life as the happiest than was true of those under 75. Opposed to these statements are the scores on the happiness attitudes, which show a tendency among both men and women for the happy attitudes to decrease with age and the unhappy attitudes to increase.

Another approach at evaluation of personal adjustment was to gauge the feeling of zest in living. Zest was measured by a combination of ten statements, each of which showed unusual enjoyment of life, yielding scores running from 0 to 10. Actual scores varied from 0 to 9. Some of the statements included were: I still feel young and full of spirit; I do as good work now as ever; I am enjoying life to the full. The scores tended to cluster at the zestful end of the scale, showing that most old people still feel the pulse of life strong within them. When, for the miscellaneous occupational group, the scores were distributed according to five-year age periods, zestfulness declined steadily with age. Forty-nine per cent of the men in their early sixties had great zest for life, but only 28 per cent of those in the late eighties (perhaps one should marvel that so high a percentage of octogenarians felt zestful). Conversely the very low scores, showing little or no zest for life increased over the same period from 12 per cent to 39 per cent. The increase was not regular, however; age 65 to 69 (when many men are adjusting to retirement) had a percentage of 22 without zest—higher than for any other period except age 85 to 89. The changes with age for women were even more marked. Zestfulness declined from 43 per cent in the early sixties to 18 per cent in the late eighties, and lack of zest increased from 18 to 57 per cent.

The total attitude inventory score

The total attitude inventory score, resulting from the addition of the scores in the ten categories of health, family, friendships, leisure, organizations, work, security, religion, usefulness and happiness, has varying relationships to its component parts. The scores for each category were correlated with the total attitude scores, and the results are shown in table 3. Corresponding correlation coefficients for 100 representative cases are given in (4) for eight of the ten categories, as follows: health, .70; friends, .55; work, .75; security, .75; religion, .14; feeling of usefulness, .76; happiness, .84; family, .51. These coefficients are all higher than those found in the original study. They confirm the statement, however, that happiness, sense of usefulness and work are closely related to the total attitude inventory score, and that religion and the family are less significant. Security, with a low correlation in the original study, has a high cor-

relation in the later study. Assuming that the inventory measures equally well attitudes in all ten categories, we would conclude that favorable attitudes toward leisure time, happiness, sense of usefulness and work are most significant in personal adjustment, and that favorable attitudes toward religion, economic security and the family (which has ceased to exist for many old people) are less significant.

TABLE 3

Correlation of scores on the attitude inventory and scores on the individual categories, by sex

Category	Coefficient of correlation	
	Males	Females
Leisure	.73	70
Happiness	.65	64
Feeling of usefulness	.62	.60
Work	.59	.61
Friends	.56	.55
Organizations	.54	.52
Health	.48	.54
Family	.40	.37
Security	.38	.41
Religion	.35	.29

TABLE 4

Median attitude inventory scores by age and sex

Age	Men	Women
60-64	52	52
65-69	50	51
70-74	53	50
75-79	52	50
80-84	51	44
85-89	48	43

The total attitude score shows some variation with age, but less than do the scores on the individual categories. In the total score a low score on one category may be offset by a high score on another, with a general leveling effect. For the miscellaneous occupational group the median attitude inventory scores by age are shown in table 4.

OTHER STUDIES OF PERSONAL ADJUSTMENT

At the present time, the field of old age research is gaining in interest, and many projects are being planned or are in process. Personal adjust-

ment is the focusing point of a number of projects, which are here briefly described.

A comprehensive long-term study of adjustment to old age is being carried on at the University of Chicago under a research committee composed of Burgess, Goldhamer and Havighurst. Publication of results is just beginning to appear (Chapter 39 of this book and 2, 3, 9, 12, 13). Some of the specific projects under investigation are adjustment in a small middle-western community, retirement in selected occupational groups, attitudes of younger people toward older, isolation of older people, employment in old age, adjustment in institutional homes, adjustment in different social classes and adjustment of the chronically ill.

Another series of studies, many closely related to personal adjustment in old age, is being conducted under the direction of Raymond G. Kuhlen at Syracuse University (5). The studies include the cultural definitions and conceptions of age periods including old age, attitudes toward old age, Rorschach testing, age trends in activities and relation of intellectual level in later maturity to maintenance of active interests.

The Moosehaven Research Laboratory maintained by the Loyal Order of Moose at Moosehaven, Florida, is carrying on various projects including a comparison of old people making high and low scores on a modification of the attitude inventory described in this chapter (5).

A study of adjustment of annuitants under the Teachers Insurance and Annuity Association has been reported by Moore, in which degree of satisfaction is used as the criterion of adjustment (5). Associated with a high degree of satisfaction are many and varied interests and hobbies. Many other items are covered in the questionnaire used but are not reported in relation to degree of satisfaction.

An early study by Morgan that compared happy with unhappy old people linked happiness with good health, pleasant emotional and social ties, hobbies, independence of living arrangements and useful work (8). A somewhat similar study of Iowans, made by Landis, used a simple measure of personal adjustment (7). Poor adjustment was found to be associated with low educational level, divorce or separation and to a lesser degree unmarried status or widowhood, poor health, unemployment in the case of men, feeling that work is a burden, lack of activities and failure to attend church. Finances and health constituted the chief worries of the group studied. A small but thorough study of 49 retired rural Pennsylvanians used an adjustment score based on fifteen items of satisfaction (10). The highest average adjustment scores were found among those who lived in the home of a relative, were married with living children and were in comfortable financial condition. Many other phases of life are covered

but *not related to the adjustment scores. Similar limited studies* are reported from time to time.

PROGRAMS CONTRIBUTING TO PERSONAL ADJUSTMENT

No one can unreel the years and bring back to old people the vigor and enthusiasm of their youth. The years pass with inexorable regularity, death is the final goal. But there is no reason why the last ten to twenty years of life need to be lived as though death had already laid its hand on the shoulder of the old. The community should not impose and the old should not accept the verdict that at age 65 or 70 the normal life of the adult must end and a half-life called old age must begin. Modifications in the *mode of living often are necessary, it is true, and often the community* of younger adults must help the old to find substitute activities and satisfactions. A definite beginning to supportive programs for the old has been made by local community and welfare agencies as well as through some state and federal welfare systems. The programs briefly described below are illustrative of what is being done and in no sense constitute a complete listing.

Health

Health is a basic factor in personal adjustment, especially in old age. Research in physical processes and in diseases of the old, carried on in *many medical schools and universities, determines the ultimate progress* that may be made to help the old to adjust to physical conditions. The recent establishment of *Geriatrics* and the *Journal of Gerontology* and the publication of this and other books in the field are proof of the growing interest. On the national level, the Unit on Gerontology and the Division of Chronic Disease of the United States Public Health Service and the recently organized Commission on Chronic *Illness* make their contribution. States are also aware of the problem. Illinois, for example, since 1945 has encouraged county almshouses to convert into nursing homes meeting standards set by the Illinois Public Aid Commission by providing that men and women receiving Old Age Assistance may use their pensions to pay for care in the county nursing home; formerly the county home resident was supported locally by the township in which he resided. The result

search Hospital which sp...

mental patients. Increased care in licensing of private nursing homes also leads to improved care.

Family relationships

Departed and dead members of families cannot be restored. Adult children cannot be forced to include aged parents and relatives in their family circle. Substitutions are the institutional home, the private nursing home and foster-home care. Because many old people are physically or mentally unable to demand proper surroundings and care, supervision of the various types of homes is necessary. Licensing, constant inspection and supervision by welfare agencies are necessary but in many communities are still inadequate. In some states nursing home proprietors have organized voluntary professional associations which will gradually improve standards.

Foster-home care is perhaps the best substitute for the family. As developed by the Jewish Social Service Bureau of Chicago, the plan uses many of the safeguards previously devised for placement of children. Families are sought that are willing to include the old person in the family life and give warmth of companionship as well as provide room and board.

Recreation

Recreation for the elderly has probably had the most rapid and successful expansion of any of the programs for the old. Little expenditure of money is required and volunteers may be widely used to guide the programs. Philadelphia, with a city-wide professional recreation leader and more than forty clubs for old people, is outstanding. The William Hodson Community Center in the Bronx, exclusively for old people, makes another approach to recreation. Cities too numerous to mention have clubs, hobby shows, craft centers, special interest groups organized under individual community centers, councils of social agencies or departments of public welfare. The programs of these groups serve several functions—they break into the monotony of full-time leisure, develop new interests and skills, give a sense of status and importance and set the stage for many new friendships that replace old ties broken by death, change of residence and loss of occupation.

Employment

Little has been done to adjust employment to old people. In fact, the philosophy has become widely accepted that at age 65 the employed should stop work, regardless of desire or physical condition. Nevertheless the experience of individual industries that have continued to employ older workers and the return of oldsters to work during the Second World War point to the need for research in this area and a new conception of when a man or woman becomes unemployable.

Security

Increasing economic security was one of the first wide-scale programs to be initiated for the old. When the Social Security Act was passed in 1935, those over 65 without resources were assured of minimum financial security. Old Age and Survivor's Insurance gave a degree of security to those employed in certain occupations (the coverage was greatly increased in 1950) through an insurance plan to which employee and employer contributed, while Old Age Assistance provided for those without any income or a very small income. Recently, industrial pensions have been established by many large industries and employers are gradually accepting a new concept of responsibility for long-term workers after retirement. Through these and other public and private welfare measures, security of the old is improving.

Religion

The increased interest in religion that old people show as age increases indicates that churches might play an important role both in providing social contacts and in helping old people to reorganize their attitudes and achieve an acceptance of old age. Undoubtedly individual churches give attention to old people among their members, but church associations or denominations have not assumed leadership that goes beyond pensions for retired ministers and their widows and occasionally homes for ministers or members of the denomination. Welfare agencies both public and private, medical schools and industry are now assuming leadership; none of these agencies is equipped to do what the church might do—develop a new philosophy of old age.

Counselling

Slowly, special counselling centers that specialize in problems of old age are being developed. With the exception of a few centers operated privately by psychologists, this service tends to be sponsored by a central welfare association, such as the council of social agencies. The public agencies that administer Old Age Assistance do a certain amount of case work with their clients, and social agencies and clinics in general are becoming more aware of the needs of older people.

Public awareness

All the movements and programs outlined aid in personal adjustment of the old. But perhaps of even greater importance is the growing public awareness of the existence of old people as an increasing proportion of the population. Of great significance are the conferences on old age held by

the University of Michigan, the University of Chicago, the University of Kansas, Washington University School of Medicine, the Social Science Research Council and other institutions, as well as the national conference held by the Federal Security Agency. Radio programs, feature stories in newspapers, magazine articles and books for the laymen are making the public old-age conscious. One result is willingness on the part of the public to support programs to aid old people; another will be more careful planning on the part of the present middle-aged group for their own old age.

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